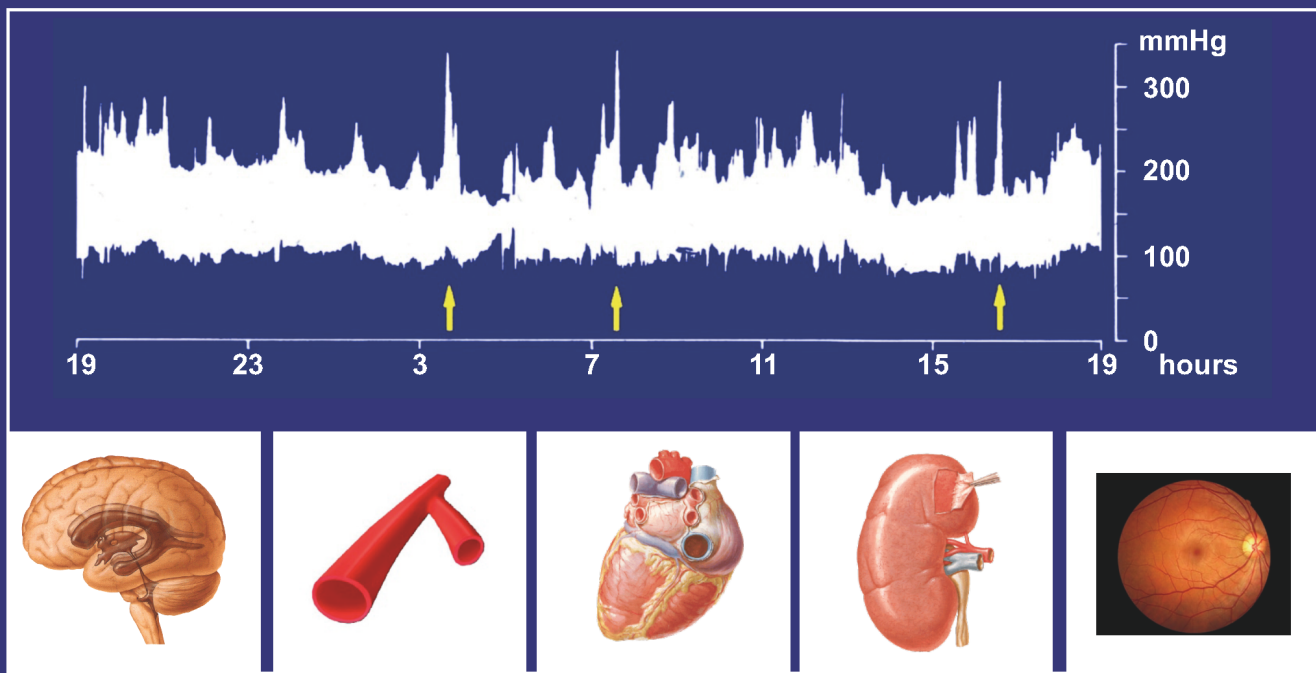




# Manual of Hypertension of the European Society of Hypertension

Third Edition

Edited by

**Giuseppe Mancia, Guido Grassi,  
Konstantinos P. Tsioufis, Anna F. Dominiczak,  
and Enrico Agabiti Rosei**

THIRD EDITION

# **Manual of Hypertension**

of the **European Society of Hypertension**



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THIRD EDITION

# Manual of Hypertension

of the European Society of Hypertension

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# Introduction

We are delighted to present to doctors and students of hypertension and related cardiovascular diseases the third edition of the *Manual of Hypertension of the European Society of Hypertension*. As in the previous editions, the epidemiological, pathophysiological, diagnostic and treatment aspects of hypertension are addressed in detail by recognized experts in this important area of medicine. This edition of the *Manual*, however, also includes chapters on the emerging aspects of hypertension which are of great current interest, either because of the mechanistic, diagnostic and treatment openings provided by basic and clinical research, or because results are somewhat inconsistent or even controversial, leading to differences in opinion within the medical community.

The recent hypertension guidelines of the European Society of Cardiology and the European Society of Hypertension are also included to provide the reader less interested in research details and more in the daily management of the high blood pressure condition with information on how to deal with hypertension in clinical practice.

Hypertension represents a success story for modern medicine. Although the causes of the blood pressure elevation remain in most individual patients almost as obscure in the third millennium as they were a century ago, mechanistic research has allowed us to discover most of the systems involved in cardiovascular control known today, while clinical hypertension research has pioneered the era of randomized outcome-based trials, documenting

the beneficial effects of antihypertensive treatment in virtually all hypertension phenotypes well ahead of a similar achievement in diabetes or dyslipidemias. Yet, several important problems remain unresolved, above all the fact that, despite the availability of a large number of effective antihypertensive drugs and drug combinations, blood pressure control by treatment remains disappointingly low, which keeps hypertension still the most important cause of mortality worldwide. This depends on the barriers to effectiveness of treatment that characterize clinical practice, such as low adherence to the prescribed treatment regimen and therapeutic inertia. As the readers will see, this is the object of great attention in the *Manual*, which devotes much more space than in the past to the problems posed by real-life hypertension management as well as by the optimization of the follow-up of treated hypertensive individuals.

We express our deep gratitude to the authors of the chapters for the time and effort they have devoted to this book, as well as for the scientific excellence of their contributions. We are sure that this will make the *Manual* useful and pleasant reading.

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Guido Grassi  
Konstantinos P. Tsioufis  
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# Section I

## Background and Epidemiology

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# HISTORY OF THE EUROPEAN SOCIETY OF HYPERTENSION: PAST, PRESENT AND FUTURE

1

Konstantinos P. Tsioufis and Enrico Agabiti Rosei

## INTRODUCTION

The European Society of Hypertension (ESH) is the leading European platform for scientific exchange in hypertension. The society is committed to excellence in research, education and clinical practice in hypertension and cardiovascular prevention with an aim to reduce hypertension-induced morbidity and mortality.

The history of the ESH spans more than three decades, and its coming of age has coincided with the great progress in research and clinical management of the complex entity that hypertension has proven to be (1). The first seeds of the ESH were planted in the 1980s. At that time, the International Society of Hypertension (ISH) encouraged the development of parallel activities in Europe. A group of hypertension experts led by Professor Alberto Zanchetti coordinated European Hypertension Meetings in Milan (the so-called 'Milan Meetings') in the years that the ISH did not hold its biennial meetings. The first meeting, organized by a European programme committee led by Alberto Zanchetti and Giuseppe Mancia as secretary, took place in the historic University of Milan during 29th May–1st June 1983. The meeting was met with enthusiasm, evident from the large number of abstracts received and the impressive number of experts from 40 attending countries. Two more meetings followed (in 1985 and 1987), again with great success. The profound interest in these meetings to exchange knowledge in clinical hypertension research was the trigger for an official European organization for hypertension.

The official birthdate of the ESH took place in 24, February, 1989. It was then that European hypertension experts established the organization, with Professor Willem Birkenhäger (1927–2013) being the first ESH president. The 4th European Hypertension Meeting, in Milan on 18–21 June 1989, was the first to be organized under the auspices of the ESH.

The ESH may safely be regarded as the young sibling of the ISH. The regulations and aim are similar; European members of the ISH would also be members of the ESH, and the two societies would share at different times the same experts in their respective scientific boards. Notably, the *Journal of Hypertension* is the official journal of both the ESH and ISH.

During the 1990s, it would be clear that the ESH was an ever-growing society. The biennial meetings received an increasing number of abstracts and participants, reaching the impressive numbers of up to 1160 and 4340, respectively, in 1999. Attendees were from throughout Europe as well as the Americas, Asia, the Middle East and North Africa. In 1999, it was thus decided that the ESH meeting would be held annually and in larger premises than the dazzling but relatively small University of Milan (established in 1915); meetings were subsequently to be held in other European cities (starting with Göteborg in 2000) and in Milan every second year.

By 2018, the ESH has grown to be a large network with a meticulously defined infrastructure. The latter includes the ESH council board comprising of executive officers and members, as well as active working groups and associated hypertension societies and centres throughout Europe and other continents (Table 1.1). The year of this writing (24 March 2018), Professor Alberto Zanchetti passed away at the age of almost 92 years. As it was written by G. Mancia in his memoriam on behalf of all Professor Zanchetti's pupils, Alberto Zanchetti will remain in memory as a great scientist and a great man. He was instrumental in the creation and growth of ESH, he was the originator and organizer of many ESH meetings, and he was the driving force, behind the European hypertension guidelines.

## ACTIVITIES AND TRAINING

### ANNUAL MEETING ON HYPERTENSION

It is evident that the history of the annual meetings of the ESH has been strongly intertwined with the course of the organization itself. The meetings offer a high-quality opportunity for attendees to be exposed to the latest basic and clinical research as well as clinical practice updates in hypertension. Multiple teaching sessions, state-of-the-art lectures, poster and oral abstract presentation sessions comprise the scientific programmes. Pre- and post-ESH



**Table 1.1** Structure of the ESH

|                                                                         |
|-------------------------------------------------------------------------|
| ESH Council Board                                                       |
| 35 ESH Affiliated National Hypertension Societies                       |
| 5 ESH Associated National Hypertension Societies                        |
| 191 ESH Excellence Centres – 179 in Europe/12 in non-European countries |
| 1069 ESH Hypertension Specialists in 49 countries                       |
| 12 ESH Working Groups                                                   |

meeting satellite symposiums are also offered around Europe to provide further knowledge on topics of general and special interest.

## WORKING GROUPS

There are 12 Working Groups of the ESH that have been created for the study of specific topics in the fields of experimental and clinical hypertension (Table 1.2). Their purposes are to gather and communicate scientific information, to promote and organise research and to establish specific recommendations. Comprising of a chairman, a secretary and members including experienced scientists and young investigators, the ESH Working Groups are principal contributors to the activities of the Society by proposing subjects for scientific research and by initiating multicentre studies requiring the cooperation of university and non-university centres in Europe.

## SUMMER SCHOOLS AND COURSES

As education is a primary target of the ESH, a number of educational activities deserve specific mention. Firstly, The ESH

Summer School started in 1995, its predecessor being a summer school organized by the German Hypertension Society in Heidelberg in 1991. Targeted towards younger candidates—preferably below 40 years of age—devoted to hypertension basic research or clinical practice, the ESH Summer School provides a unique combination of educational sessions from international experts, opportunity for social networking and exposure to beautiful destinations across Europe.

For more experienced scientists, the ESH also organizes advanced courses on hypertension for certified European hypertension specialists or those who wish to become so in the near future. Educational master courses for hypertension leaders are also held to present and analyse all recent progress in hypertension and cardiovascular prevention.

## THE WEB PORTAL AND APPLICATIONS

The ESH Web portal was presented in the ESH annual meeting in Milan in 2001 as a means to support the activities of the ESH and to present all things relevant to the society through the rapidly growing worldwide web. Today, the website [www.eshonline.org](http://www.eshonline.org) provides all needed information regarding the ESH organization, the activities of the working groups and its scientific sessions, and also has direct access to guidelines, newsletters and other scientific material. Most importantly, its e-learning platform offers selected educational resources to both ESH members as well as non-members, including self-assessment programs.

In the attempt to improve doctor-patient interaction and to increase awareness on hypertension and its associated risks, the ESH in collaboration with the Italian Society of Hypertension has published a dedicated application for smartphones and tablets. This application, ESH CARE, can be found at the ESH portal and is the only application on hypertension currently validated and supported by the European Society of Hypertension.

## HYPERTENSION SPECIALIST PROGRAMME

The ESH Hypertension Specialist Programme was started in 2000 aimed towards hypertension specialists in Europe, to further enhance their expertise and eventually to improve hypertension management in European countries. The ESH specialists should be members of the ESH, having clinical experience in difficult hypertension, documented recognized scientific activity and continuous interest in hypertension. More than 1000 ESH Specialists have been approved following nominations by national societies.

## CENTRES OF EXCELLENCE

In 2005 the concept of the ESH Centres of Excellence was conceived to identify institutions that by definition provide 'the highest level of both inpatient and outpatient hypertension care, including surgical and vascular interventions, and assessment of global cardiovascular risk'. There has been a significant increase of centres through the years and there are currently 191 ESH Centres of Excellence in 36 European countries, and associated centres in 7 non-European countries (Australia, Bahrain, Brazil, Israel, Lebanon, People's

**Table 1.2** Working Groups of the ESH

|                                                             |
|-------------------------------------------------------------|
| On blood pressure in children and adolescents               |
| On blood pressure monitoring and cardiovascular variability |
| On Endocrine hypertension                                   |
| On endothelins and endothelial factors                      |
| On hypertension and the brain                               |
| On hypertension and the heart                               |
| On hypertension and the kidney                              |
| On hypertension and sexual dysfunction                      |
| On hypertension, thrombosis and arrhythmias                 |
| On interventional treatment of hypertension                 |
| On obesity diabetes and the high-risk patient               |
| On vascular structure and function                          |

Republic of China and Venezuela). These centres contribute to the continuous effort of the ESH to stimulate scientific exchange in hypertension, and support and build organizations committed to enhance hypertension control worldwide. Collaboration attempts among excellence centres have been possible by sharing protocols in clinical work and research, by organizing specific sessions during the annual meetings and by centre participation in multicentre studies.

## AFFILIATED SOCIETIES

The close relationship of the ESH with national societies of hypertension has been a main priority. Therefore, the ESH has developed an affiliation and association programme to provide a formal link with national societies from European countries. The relationship between ESH and the national hypertension societies has been growing stronger over the years, and members of the ESH-affiliated societies are encouraged to participate in ESH activities. In close cooperation with them, the ESH has been expanding in activities including organization or endorsement of meetings and educational activities such as summer schools and advanced courses. There are 35 ESH-affiliated societies in Europe, and there are also five associated hypertension societies and organizations from non-European countries that have established professional relationships with the ESH.

## ESH RESEARCH PROJECTS

The Society has always focused on promoting research in the field of hypertension. As of now, a number of research programmes have been initiated and there is a call for collaboration to all centres. Current ESH research activities include the atrial fibrillation survey, the fibromuscular dysplasia registry, the multicentre study on the management of acute hypertensive events, the MASKed-unconTrolled hyperTension Management Based on Office BP or on Out-of-office (Ambulatory) BP Measurement (MASTER) study and the BP control study across Europe.

## PUBLICATIONS

### GUIDELINES

Hypertension guidelines contribute greatly to the ESH goal to reduce hypertension-induced morbidity and mortality. Prominent ESH members had contributed significantly to guidelines issued by the ISH and the World Health Organization until 1999. Considering the homogeneity in Europe with respect to its population and access to diagnostic and therapeutic options, it was decided at that time that separate European guidelines would be published. The first joint ESH/European Society of Cardiology guidelines were presented at the annual meeting in Milan in 2003, and the respective article in the *Journal of Hypertension* was widely circulated (2). The same success was noted in the following hypertension guidelines published in 2007 (including the 2009 'Reappraisal') and 2013 (3–5). An important asset of these guidelines

has always been the careful collection and evaluation of data as well as the extensive review process. The latest joint European Hypertension Guidelines were presented at the annual ESH meeting in Barcelona, June 2018, with simultaneous publication in the two official journals of ESH and ESC, *Journal of Hypertension* and *European Heart Journal*, respectively (6).

## SCIENTIFIC DOCUMENTS

The ESH has published a series of acclaimed guidelines, position statements and consensus documents covering all subjects in hypertension management: blood pressure measurement, hypertension in children and adolescents (7) and hypertension management in specific patient groups such as sleep apnea and dialysis patients, to name a few (8–11).

The ESH issues a scientific newsletters at a regular basis: *Update on Hypertension Management* has the latest news and research in many clinical topics. Sixty-three newsletters have been published between 2000 and 2016. Over the years, the ESH newsletters have been distributed as single-page documents at the ESH annual meetings and are available in PDF format on the ESH website.

## JOURNALS

Two scientific journals are endorsed by the ESH. The *Journal of Hypertension*, the official journal of the ISH and the ESH, is published monthly and spans over 200 pages. With a team of international associate editors, the journal publishes peer-reviewed, original basic and clinical research with an about one-to-three ratio, as well as review articles, guidelines, intriguing commentaries and meeting abstracts. With an impact factor of 4.085 (2016) and ranking 12th out of 63 peripheral vascular disease journals, it is a leading journal in hypertension with submissions from research centres all over the world. *Blood Pressure* is a journal dedicated to clinical hypertension research, with an editorial board that also features leading experts from Europe and the United States. This journal was introduced in 1992 and has gained increasing popularity, reaching an impact factor of 2.163 in 2016.

## BOOKS

A major goal of the ESH is to disseminate the latest information regarding optimal approaches for diagnosis, treatment and management of hypertension. *The Manual of Hypertension of the European Society of Hypertension* was first published in 2008 and is currently in its third edition. The ESH has also endorsed or co-endorsed international scientific books related to hypertension and cardiovascular prevention and therapy edited by distinguished members of the Society. In these books, topics such as preclinical organ damage, brain damage and interventional therapies of hypertension have been separately covered (12–14).

## REFERENCES

1. Zanchetti A, Cifková R, Parati G, Narkiewicz K. *European Society of Hypertension: Past, Present and Future*. Via Medica, Gdańsk; 2011.

2. European Society of Hypertension–European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; 21: 1011–1153.
3. Mancia G, De Backer G, Dominiczak A et al. ESH-ESC Task Force on the Management of Arterial Hypertension. 2007 ESH-ESC practice guidelines for the management of arterial hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. *J Hypertens* 2007; 25: 1751–1762.
4. Mancia G, Laurent S, Agabiti-Rosei E et al. European Society of Hypertension. Reappraisal of European guidelines on hypertension management: A European Society of Hypertension Task Force document. *J Hypertens* 2009; 27(11): 2121–2158.
5. Mancia G, Fagard R, Narkiewicz K et al. Task force members. 2013 ESH/ESC guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31(7): 1281–1357.
6. Williams B, Mancia G, Spiering W et al. Task Force Members. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *J Hypertension* 2018; 36: 1953–2041.
7. Lurbe E, Agabiti Rosei E, Cruickshank et al. Task Force members. European Society of Hypertension guidelines of high blood pressure in children and adolescents. *J Hypertension* 2016; 34: 1887–1920.
8. O'Brien E, Asmar R, Beilin L et al. European Society of Hypertension working group on blood pressure monitoring. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. *J Hypertens* 2005; 23(4): 697–701.
9. Lurbe E, Cifkova R, Cruickshank JK et al. European Society of Hypertension. management of high blood pressure in children and adolescents: Recommendations of the European Society of Hypertension. *J Hypertens* 2009; 27(9): 1719–1742.
10. Parati G, Lombardi C, Hedner J et al. European respiratory society; EU COST ACTION B26 members. Position paper on the management of patients with obstructive sleep apnea and hypertension: Joint recommendations by the European Society of Hypertension, by the European Respiratory Society and by the members of European COST (COoperation in scientific and technological research) ACTION B26 on obstructive sleep apnea. *J Hypertens* 2012; 30(4): 633–646.
11. Sarafidis PA, Persu A, Agarwal R et al. Hypertension in dialysis patients: A consensus document by the European renal and cardiovascular medicine (EURECA-m) working group of the European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) and the hypertension and the kidney working group of the European Society of Hypertension (ESH). *J Hypertens* 2017; 35(4): 657–676.
12. Agabiti Rosei E, Mancia G. *Assessment of Preclinical Organ Damage in Hypertension*. Springer International Publishing, Switzerland; 2015.
13. Tsioufis C, Schmieder R, Mancia G. *Interventional Therapies for Secondary and Essential Hypertension*. Springer, Switzerland; 2016.
14. Coca A. *Hypertension and Brain Damage*. Springer, Switzerland; 2016.

# HYPERTENSION AS A CARDIOVASCULAR RISK FACTOR

# 2

*Renata Cifkova and Peter J. Blankestijn*

## HYPERTENSION AS A CARDIOVASCULAR RISK FACTOR

Hypertension is the most prevalent cardiovascular disorder, affecting 20–50% of the adult population worldwide, and ranking, in a comparative risk assessment of 84 risk factors and risk factor clusters, high for global disease burden (1). Likewise, it has been identified as a risk factor for coronary heart disease, stroke, peripheral arterial disease and heart and renal failure in both men and women in a large number of epidemiological studies (2–5). Hypertension has also been shown to increase the risk of atrial fibrillation (6). In addition, observational studies have found that blood pressure (BP) correlates inversely with cognitive function and that hypertension is associated with an increased incidence of dementia (7,8).

In the year 2001, the worldwide burden of disease attributable to high systolic BP ( $\geq 115$  mmHg) was 54% for stroke, and 47% for ischaemic heart disease (9). About half of this burden was experienced by individuals with hypertension, the other part in those with a lesser degree of high BP. More than 80% of the attributable burden of the disease was found in low- and middle-income regions.

A meta-analysis of individual data of one million adults from 61 prospective observational studies found a continuous graded independent relationship with the risk of stroke and coronary events (10). Coronary heart disease (CHD) and stroke mortality increases progressively and linearly from BP levels as low as 115 mmHg systolic and 75 mmHg diastolic upward (Figures 2.1 and 2.2). The increased risks are seen in all age groups from 40 to 89 years of age. For every 20 mmHg systolic or 10 mmHg diastolic BP increase, there is a doubling of mortality from CHD and stroke.

## ASSESSMENT OF TOTAL CARDIOVASCULAR RISK IN HYPERTENSION

### INTRODUCTION

Historically, hypertension guidelines long focused on BP values as the only or main variables determining

therapeutic interventions. Although this approach was maintained in the 2003 Joint National Committee (JNC) seven guidelines (11) and was found cost effective (12), the ESH-ESC guidelines have since 2003 (13–15) emphasized that management of hypertension should be related to quantification of total cardiovascular (CV) risk. Finally, this approach was also adopted by the most recent US hypertension guidelines (16). The rationale for this approach is that only a small proportion of the hypertensive population has an elevation of BP alone with the great majority exhibiting additional CV risk factors (17–21), with a relationship between the severity of BP elevation and that of alterations in glucose and lipid metabolism (22). When elevated BP and metabolic risk factors are concomitantly present, they potentiate each other risk (17,23,24). Thresholds and goals for antihypertensive treatment as well as treatment strategies for concomitant risk factors may differ based on total CV risk. Therefore, estimation of total CV risk is essential for guiding patient management.

The use of total CV risk estimation may also improve physicians' behaviour in drug prescription and patient adherence (25,26); however, there are some reports showing no impact on provider behaviours (27) and inadequate use in routine clinical practice (28,29).

### HOW TO ASSESS TOTAL CV RISK

A number of complex and computerized methods have been developed for estimating total CV risk, that is, the likelihood of experiencing a CV event, usually within the next 10 years. Many risk stratification systems are based on the Framingham study (30), estimating the 10-year risk for both fatal and nonfatal CHD by systolic BP and presence of other risk factors. The easy and rapid calculation of the Framingham risk score using published tables (National Cholesterol Education Program [NCEP]) (31) may assist the physician and patient in demonstrating the benefits of treatment.

The Framingham risk stratification has been shown to be reasonably applicable to some European populations (32) but requiring recalibration in other populations (33,34) due to geographic differences in the incidence of coronary and stroke events.

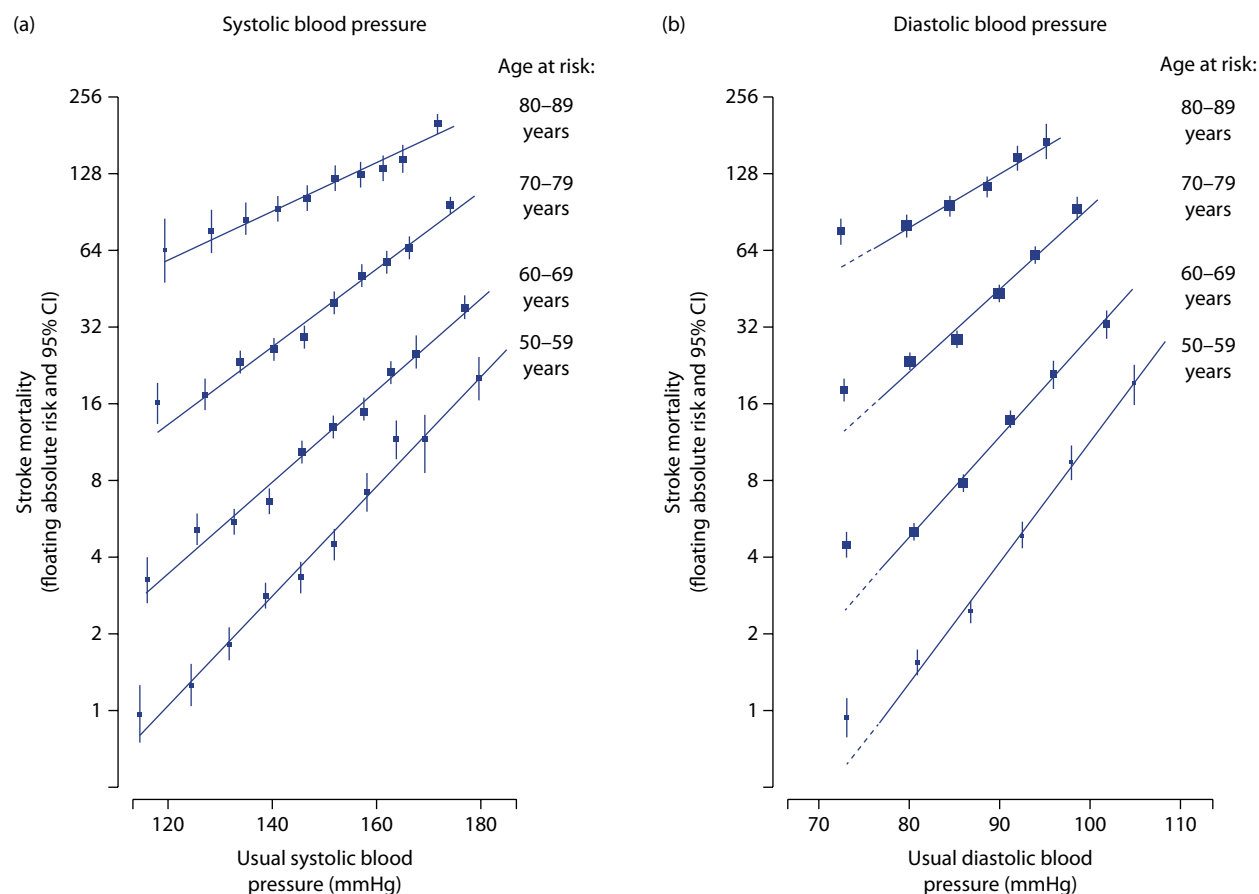


**Figure 2.1** Stroke mortality rate in each decade of age plotted for the usual systolic (a) and diastolic (b) blood pressure at the start of that decade. Data from 1 million adults in 61 prospective studies. (Adapted from Lewington S et al. *Lancet* 2002; 360(10): 1903–1913.)

The latest US hypertension guidelines (16) recommend use of the ACC/AHA Pooled Cohort Equation (<http://tools.acc.org/ASCVD-Risk-Estimator/>) to estimate the 10-year risk of atherosclerotic CVD (ASCVD) to establish the BP threshold for treatment (35).

Given the need for a European model based on a large database, the SCORE (Systemic Coronary Risk Evaluation) project (36) was used to develop SCORE charts for high- and low-risk countries in Europe estimating the risk of dying from CV (not just coronary) disease over 10 years, and allowing calibration of the charts for individual countries provided that national mortality statistics and estimates of the prevalence of major CV risk factors are available. The SCORE model has also been used in the HeartScore, the official European Society of Cardiology management tool for implementation of CVD prevention in clinical practice (<http://www.escardio.org>).

The main disadvantage associated with an intervention threshold based on relatively short-term absolute risk is that younger adults (particularly women), while having more than one risk factor, are unlikely to reach treatment thresholds despite being at high risk relative to their peers. By contrast, most elderly men (e.g., those aged 65) will often reach treatment thresholds whilst being at very little increased risk relative to their peers. This situation results in most resources being concentrated on the oldest

subjects whose potential lifespan, despite intervention, is relatively limited, while young subjects at high relative risk remain untreated despite, in the absence of intervention, a predicted significant shortening of their otherwise much longer potential lifespan (37,38).

Use of the SCORE chart for estimating total CV risk in hypertension should be considered a minimal requirement taking into account the fact that total CV risk can be underestimated (39).

On the basis of these considerations, the 2013 ESH-ESC guidelines (15) suggest total CV risk be stratified as shown in Table 2.1. The terms *low* (<1%), *moderate* ( $\geq 1$  and <5%), *high* ( $\geq 5$  and <10%) and *very high* ( $\geq 10\%$ ) risk refer to the 10-year risk of CV mortality as defined by the 2012 ESC prevention guidelines (40). The factors on which this stratification is based are listed in Table 2.2. They include risk factors, asymptomatic organ damage, diabetes mellitus and established CV or renal disease.

### SEARCHING FOR SUBCLINICAL (ASYMPTOMATIC) ORGAN DAMAGE

Given the importance of subclinical organ damage as an intermediate stage in the continuum of vascular disease



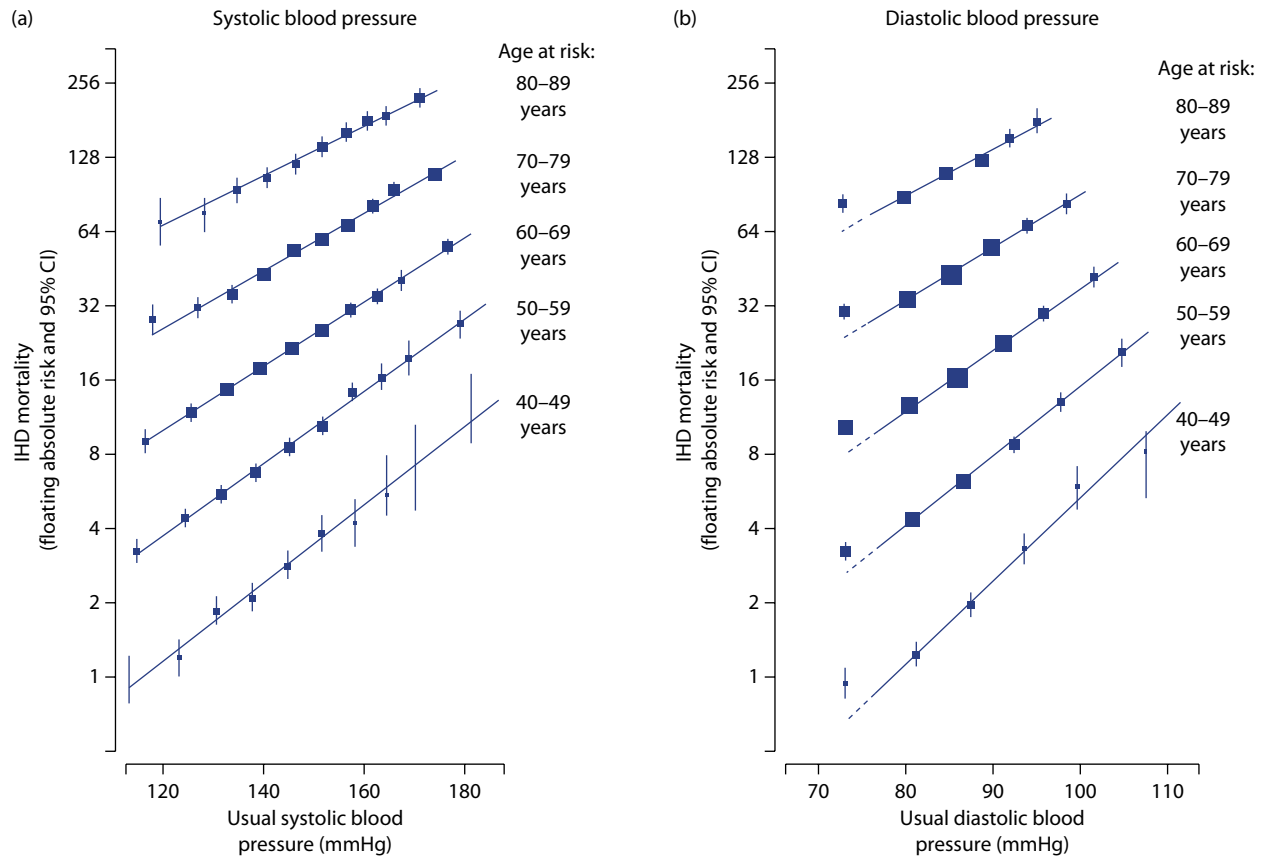


**Figure 2.2** Ischaemic heart disease (IHD) mortality rate in each decade of age plotted for the usual systolic (a) and diastolic (b) blood pressure at the start of that decade. Data from one million adults in 61 prospective studies. (Adapted from Lewington S et al. *Lancet* 2002; 360(10): 1903–1913.)

and as a determinant of overall CV risk, signs of organ involvement in hypertensive individuals should be sought for carefully, using appropriate techniques.

The presence of any of the four following markers, that is, increased urinary albumin excretion (UAE), increased pulse wave velocity (PWV), left ventricular

hypertrophy (LVH), and carotid plaques, predicts CV mortality independently of SCORE stratification (41–43). This is an argument favouring routine use of organ damage assessment, particularly in specialized centres or clinics. The risk increases with the number of damaged organs (41).

**Table 2.1** Stratification of total CV risk

| Other risk factors,<br>asymptomatic organ damage<br>or disease | Blood pressure (mmHg)                      |                                           |                                             |                                       |
|----------------------------------------------------------------|--------------------------------------------|-------------------------------------------|---------------------------------------------|---------------------------------------|
|                                                                | High normal<br>SBP 130–139<br>or DBP 85–89 | Grade 1 HT<br>SBP 140–159<br>or DBP 90–99 | Grade 2 HT<br>SBP 160–179<br>or DBP 100–109 | Grade 3 HT<br>SBP ≥180<br>or DBP ≥110 |
| No other RF                                                    |                                            | Low risk                                  | Moderate risk                               | High risk                             |
| 1–2 RF                                                         | Low risk                                   | Moderate risk                             | Moderate to high risk                       | High risk                             |
| ≥3 RF                                                          | Low to moderate risk                       | Moderate to high risk                     | High risk                                   | High risk                             |
| OD, CKD stage 3 or diabetes                                    | Moderate to high risk                      | High risk                                 | High risk                                   | High to very high risk                |
| Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs          | Very high risk                             | Very high risk                            | Very high risk                              | Very high risk                        |

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HT = hypertension; OD = organ damage; RF = risk factor; SBP = systolic blood pressure.

**Table 2.2** Factors – other than office BP – influencing prognosis; used for stratification of total CV risk*Risk factors*

- Male sex
- Age (men  $\geq 55$  years; women  $\geq 65$  years)
- Smoking
- Dyslipidemia
  - Total cholesterol  $>4.9$  mmol/L (190 mg/dL); and/or
  - LDL-cholesterol  $>3.0$  mmol/L (115 mg/dL); and/or
  - HDL-cholesterol: men  $<1.0$  mmol/L (40 mg/dL), women  $<1.2$  mmol/L (46 mg/dL); and/or
  - Triglycerides  $>1.7$  mmol/L (150 mg/dL)
- Fasting plasma glucose 5.6–6.9 mmol/L (102–125 mg/dL)
- Abnormal glucose tolerance test
- Obesity (BMI  $\geq 30$  kg/m<sup>2</sup>)
- Abdominal obesity (waist circumference: men  $\geq 102$  cm, women  $\geq 88$  cm in Caucasians)
- Family history of premature CV disease (men aged  $<55$  years; women aged  $<65$  years)

*Asymptomatic organ damage*

- Pulse pressure (in the elderly)  $\geq 60$  mmHg
- Left ventricular hypertrophy
  - Electrocardiogram: Sokolow-Lyon index  $>3.5$  mV; RaVL  $>1.1$  mV; Cornell voltage duration product  $>244$  mV  $\times$  ms; or
  - Echocardiogram: LVM index<sup>a</sup>: men  $>115$  g/m<sup>2</sup>; women  $>95$  g/m<sup>2</sup>
- Carotid wall thickening (IMT  $>0.9$  mm) or plaque
- Carotid-femoral pulse wave velocity  $>10$  m/s
- Ankle-brachial index  $<0.9$
- CKD with eGFR (30–60 mL/min/1.73 m<sup>2</sup>)
- Microalbuminuria
  - 30–300 mg/24 h or albumin-creatinine ratio 30–300 mg/g;
  - 3.4–34 mg/mmol preferentially in morning spot urine

*Diabetes mellitus*

- Fasting plasma glucose  $\geq 7.0$  mmol/L (126 mg/dL) on 2 repeated measurements; and/or
- HbA<sub>1c</sub>  $>7\%$  (53 mmol/mol); and/or
- Post-load plasma glucose  $>11.0$  mmol/L (198 mg/dL)

*Established CV or renal disease*

- Cerebrovascular disease:
  - Ischaemic stroke
  - Cerebral haemorrhage
  - Transient ischaemic attack
- CHD:
  - Myocardial infarction
  - Angina
  - Coronary revascularization with PCI or CABG
  - Heart failure
- Heart failure, including heart failure with preserved EF
- Symptomatic lower extremities PAD
- CKD with eGFR  $<30$  mL/min/1.73 m<sup>2</sup>; proteinuria ( $>300$  mg/24 h)
- Advanced retinopathy:
  - Haemorrhages or exudates
  - Papilledema

Source: Adapted from Mancia G et al. *J Hypertens* 2013; 31(15): 1281–1357.

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CHD, coronary heart disease; CKD, chronic kidney disease; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, glycated hemoglobin; HDLC, high-density lipoprotein cholesterol; IMT, intima-media thickness; LDL-C, low-density lipoprotein cholesterol; LVM, left ventricular mass; PCI, percutaneous coronary intervention; PWV, pulse wave velocity.

<sup>a</sup> Risk maximal for concentric LVH: increased LVM index with a wall thickness to radius ratio of 0.42.

**HEART****ELECTROCARDIOGRAPHY**

Electrocardiography (EKG) is part of routine assessment of hypertensive individuals in order to detect LVH, pattern of 'strain', ischemia and arrhythmias. Its sensitivity in detecting LVH is low; nonetheless hypertrophy detected by Sokolow-Lyons index, modified Sokolow-Lyons index (largest S wave plus largest R wave  $>3.5$  mV) or by Cornell voltage QRS duration is an independent predictor of CV events (44). In a prospective survey including 7495 American adults, a new indicator of LVH, the Novacode estimate of left ventricular mass index (LVMI) (based on both voltage and strain pattern criteria), has been reported to be significantly related to 10-year CV mortality (45). A further analysis from the LIFE (Losartan Intervention For Endpoint reduction in hypertension) trial has shown that hypertensive patients with EKG LVH or left bundle branch block are at increased risk of CV mortality and hospitalization for heart failure (46). A prospective study by Verdecchia et al. (47) documented that R-wave voltage in aVL is closely associated with left ventricular mass (LVM) and predictive of CV events when hypertension is not accompanied by EKG LVH. The prevalence of EKG LVH increases the severity of hypertension (48).

Electrocardiography seems to be valuable at least in patients over 55 years of age (49,50). Electrocardiographic ST-T abnormalities are often present in conjunction with EKG LVH. Adding EKG repolarization changes to EKG voltage and QRS duration may improve the detection of LVH (51). It can also be used to detect LV strain indicating higher risk (44,49). In the LIFE study, new development of EKG strain was a strong predictor of adverse outcome in the setting of EKG LVH regression (52).

Longer QRS duration is an independent predictor of sudden cardiac death and heart failure in patients with hypertension (52,54).

Electrocardiography and/or 24-hour Holter EKG monitoring play crucial roles in detecting atrial fibrillation, an independent predictor of adverse outcomes such as stroke, heart failure and CV mortality in hypertensive patients (55). There is growing evidence that new-onset atrial fibrillation should be considered target-organ damage (56).

**ECHOCARDIOGRAPHY (TWO-DIMENSIONAL TRANSTHORACIC)**

Standard two-dimensional transthoracic echocardiography (2D-TTE) is more sensitive than electrocardiography in diagnosing LVH (57) and predicting CV and renal risk (58); it may also be more helpful in risk stratification (59).

There are also some technical limitations such as inter-observer variability, low-quality imaging in obese individuals and in patients with obstructive lung disease. Although the relation between LVMI and CV risk is continuous, thresholds of 115 g/m<sup>2</sup> for men and 95 g/m<sup>2</sup> for women are widely used for conservative estimates of LVH (60). Concentric hypertrophy (wall-to-radius ratio  $\geq 0.42$  with an increased LVM), eccentric hypertrophy (increased LVM and wall-to-radius ratio  $<0.42$ ), and concentric remodelling (wall-to-radius ratio  $\geq 0.42$  with normal LVM) all predict an increased incidence of CVD, but concentric hypertrophy has consistently been shown to be associated with the highest risk (61–63).

In addition, echocardiography is a tool for assessing left ventricular systolic and diastolic function; ejection

**Table 2.3** Definitions of LVH, concentric geometry, left ventricular chamber, systolic/diastolic function and LA dilation

| Parameter              | Measure                                                 | Cutoff point               |
|------------------------|---------------------------------------------------------|----------------------------|
| LVH                    | LV mass/height <sup>2</sup> (g/m <sup>2</sup> )         | Men > 50<br>Women > 47     |
| LVH                    | LV mass/BSA (g/m <sup>2</sup> )                         | Men > 115<br>Women > 95    |
| LV concentric geometry | RWT                                                     | ≥0.43                      |
| LV chamber size        | LV end-diastolic diameter/<br>height (cm/m)             | Men > 3.3<br>Women > 3.4   |
| Systolic function      | LV ejection fraction (%)                                | >55                        |
| Diastolic function     | Septal e' velocity (cm/s)<br>Lateral e' velocity (cm/s) | <8<br><10                  |
| LV filling pressures   | E/e' (averaged) ratio                                   | ≥13                        |
| LA size (Simpson)      | LA volume/BSA (mL/m <sup>2</sup> )                      | ≥34                        |
| LA size (elliptical)   | LA volume/height <sup>2</sup> (mL/m <sup>2</sup> )      | Men > 17.7<br>Women > 16.7 |

Abbreviations: BSA, body surface area; LA, left atrial; LV, left ventricular; LVH, left ventricular hypertrophy; RWT, relative wall thickness.

fraction as well as midwall fractional shortening have been proposed as possible additional predictors of CV events. Alterations of diastolic function (i.e. alterations of LV relaxation and filling) are frequent in hypertensives, and particularly in the elderly (64). Hypertension-induced diastolic dysfunction is associated with concentric geometry and can induce symptoms/signs of heart failure, even when ejection fraction (EF) is still normal (heart failure with preserved EF) (65). Diastolic dysfunction is associated with increased risk of atrial fibrillation (66), heart failure (67) and increased total mortality (68). Filling abnormalities can be quantified by Doppler transmitral inflow pattern and predict heart failure and all-cause mortality (67,69).

Finally, echocardiography provides information on the size of the left atrium; left atrial enlargement is associated with a higher risk of atrial fibrillation, CVD and death (70–73).

Normal ranges and cutoff values of parameters to be included in the echocardiographic report are listed in Table 2.3.

Subclinical systolic dysfunction can be assessed using speckle-tracking echocardiography to quantify longitudinal contractile function (longitudinal strain).

## OTHER CARDIAC IMAGING TECHNIQUES

While three-dimensional echocardiography (3DE) is a more reliable method for quantitative analysis, and for LVM in particular, there is limited evidence for 3DE reference values and prognostic validation (74).

Cardiac magnetic resonance imaging is the gold standard for cardiac anatomical and functional quantification; it has the same limitations as 3DE and is more expensive. Cardiac magnetic resonance imaging should be used when 2D-TTE or 3DE is unavailable and LV geometry is important for the decision to treat.

## BLOOD VESSELS

### CAROTID ARTERIES

Ultrasound examination of the carotid arteries with measurement of intima-media thickness (IMT) or the presence of plaques have been shown to predict stroke and myocardial infarction (75,76). The relationship between carotid IMT and CV events is a continuous one but, for the common carotid arteries, an IMT >0.9 mm is considered abnormal (77). Ultrasound scans limited to the common carotid arteries (an infrequent site of atherosclerosis) are likely to measure vascular hypertrophy only, whereas assessment of atherosclerosis also requires scanning of the bifurcations and/or internal carotids where plaques are more frequent (78–80). Further analysis from European Lacidipine Study on Atherosclerosis (ELSA) (81) has shown baseline carotid IMT (both at carotid bifurcations and at the level of the common carotid artery) predicts CV events independent of BP (clinic and ambulatory). This suggests that both atherosclerosis (reflected by the IMT at bifurcations) and vascular hypertrophy (reflected by the common carotid IMT) exert an adverse prognostic effect in addition to that of high BP.

Quantitative B-mode ultrasound of carotid arteries requires training and methodological standardization for IMT measurement. Lack of standardization regarding the definition and measurement of IMT were responsible for high variability and low intra-individual reproducibility. A meta-analysis failed to show any added value of IMT compared with the Framingham risk score in predicting future CVD even in the intermediate risk group (82). Thus, the 2016 European guidelines on CVD prevention in clinical practice do not recommend systematic use of carotid IMT to improve risk assessment (83).

Presence of a plaque can be identified by an IMT >1.3 or 1.5 mm, or by a focal increase in thickness of 0.5 mm or 50% of the surrounding IMT value (78–80). There is evidence that, in untreated hypertensive individuals without target-organ damage by routinely performed tests, these alterations are common and thus carotid ultrasound examination may often detect vascular damage and make risk stratification more precise (39). An adverse prognostic significance of carotid plaques (hazard ratio 2.3) has also been reported in a sample of Copenhagen county residents free of overt CVD, followed for about 13 years (84).

Carotid plaque has a stronger predictive value for both stroke and myocardial infarction, higher than that of IMT and independent of traditional CV risk factors. The presence of a carotid plaque automatically reclassifies patients from intermediate to high risk (77); however, routine carotid ultrasound imaging is not recommended unless there is a clinical indication (bruit, previous TIA or stroke).

### ANKLE-BRACHIAL INDEX

A low ankle-brachial index (ABI, <0.9) signals peripheral arterial disease and, in general, advanced atherosclerosis (85,86), whereas carotid IMT measurements are able to detect earlier changes. A reduced ABI (<0.9) relates to further development of angina, myocardial infarction, congestive heart failure, need for coronary artery bypass surgery, stroke, carotid and peripheral vascular surgery (87–90) and in patients with multivessel coronary disease, it confers additional risk (91).



## PULSE WAVE VELOCITY

Large artery stiffening has been identified as the most important pathophysiological determinant of isolated systolic hypertension and age-related pulse pressure increase (92). Measurement of carotid-femoral pulse wave velocity (PWV) provides a comprehensive noninvasive assessment of arterial stiffness (93). Carotid-femoral PWV is currently considered the gold standard for large artery stiffening, a measure shown to have an independent predictive value for all-cause mortality and CV morbidity, coronary events and strokes in patients with uncomplicated essential hypertension (94–98). Reference values for PWV are available from 16,867 subjects enrolled in 13 different centres in eight European countries (99). A PWV >10 m/s is considered a conservative estimate of an abnormal value in middle-aged hypertensive patients (100). The additive predictive value of PWV beyond traditional risk scoring systems (including SCORE and the Framingham Risk Score) has been shown by the Copenhagen county population (84).

Indirect indices of aortic stiffness and wave reflection such as central blood pressure and augmentation index have been confirmed as independent predictors of CV events in two studies (101,102). In one of these studies, only central systolic blood pressure consistently and independently predicted CV mortality after adjustment for various CV risk factors including LVM and carotid IMT (102). In the Conduit Artery Function Evaluation (CAFE) study, a substudy of Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), central pulse pressure was significantly associated with a post hoc-defined composite outcome of fatal

CV events/procedures and development of renal impairment (103). The BP GUIDE study (104) showed that management of hypertension guided by central aortic blood pressure (compared with best practice care) was associated with less use of medication to achieve BP control.

In conclusion, PWV may be useful in refining risk stratification in selected patients but is not yet recommended for routine practice.

## KIDNEY

The diagnosis of induced renal damage is based on the finding of a reduced renal function and/or the detection of elevated UAE (105). Renal function is represented mainly by glomerular filtration rate (GFR) depending on the number and function of nephrons and decreasing with age after the third decade (progressive loss of 1% per year).

Renal function is currently classified based on the estimated glomerular filtration rate (eGFR) calculated using various formulas, of which the 2009 CKD EPI formula seems to be the most reliable for a wide range of patients (106). Values of eGFR <60 mL/min/1.73 m<sup>2</sup> indicate chronic kidney disease (CKD) stage 3, whilst values <30 and <15 mL/min/1.73 m<sup>2</sup> indicate CKD stages 4 and 5 (kidney failure), respectively (107) (Table 2.4).

A reduction in GFR and an increase in CV risk are also reflected in increased serum cystatin C (108).

While elevated serum creatinine or low eGFR (or creatinine clearance) indicate reduced glomerular filtration, an

**Table 2.4** Prognosis of CKD by GFR and albuminuria category

| Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012         |     |                                  |       | Persistent albuminuria categories description and range |                             |                          |
|------------------------------------------------------------------------|-----|----------------------------------|-------|---------------------------------------------------------|-----------------------------|--------------------------|
|                                                                        |     |                                  |       | A1                                                      | A2                          | A3                       |
|                                                                        |     |                                  |       | Normal to mildly increased                              | Moderately increased        | Severely increased       |
|                                                                        |     |                                  |       | <30 mg/g<br><3 mg/mmol                                  | 30–300 mg/g<br>3–30 mg/mmol | >300 mg/g<br>>30 mg/mmol |
| GFR categories (mL/min per 1.73 m <sup>2</sup> ) description and range | G1  | Normal or high                   | ≥90   |                                                         |                             |                          |
|                                                                        | G2  | Mildly decreased                 | 60–89 |                                                         |                             |                          |
|                                                                        | G3a | Mildly to moderately decreased   | 45–59 |                                                         |                             |                          |
|                                                                        | G3b | Moderately to severely decreased | 30–44 |                                                         |                             |                          |
|                                                                        | G4  | Severely decreased               | 15–29 |                                                         |                             |                          |
|                                                                        | G5  | Kidney failure                   | <15   |                                                         |                             |                          |

Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red, very high risk.

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

increase in urinary albumin or protein excretion reflects derangement in the glomerular filtration barrier. UAE has been shown to predict the development of overt diabetic nephropathy in both type 1 and 2 diabetics (109), while the presence of overt proteinuria generally indicates the presence of established renal parenchymal damage (110). Urinary albumin excretion, even below the current threshold values, has been shown to predict CV events in both diabetic and nondiabetic hypertensive patients (111,112). There is a continuous relationship between CV and non-CV mortality and urinary protein excretion (113,114). Albuminuria can be measured from spot urine samples, preferably early morning urine (24-hour or night urine samples are discouraged due to the inaccuracy of urine collection) by indexing the urinary albumin concentration to the urinary creatinine concentration (107).

Progressive reduction in eGFR and increased albuminuria indicate progressive loss of renal function towards end-stage renal disease and are both independent predictors of increased CV risk in diabetic and nondiabetic kidney disease (115). The presence of both increased albuminuria and reduced eGFR is associated with a greater risk of renal and CV complications (Table 2.4).

Hyperuricemia is frequently seen in untreated hypertensives (particularly in pre-eclampsia) and has also been shown to correlate with reduced renal blood flow and in the presence of nephrosclerosis (116).

Serum creatinine, eGFR and urinalysis, including measurement of albumin-to-creatinine ratio, are considered routine laboratory tests to be performed in all hypertensive patients and to be repeated at least annually.

## RETINAL VESSELS

Most hypertensive patients usually present early in the process of their disease, and haemorrhages and exudates (grade 3) and papilledema (grade 4) are observed very rarely but are highly reproducible and always associated with an increased risk of CV events (117,118). On the other hand, grade 1 (focal or general arteriolar narrowing) and 2 (arteriovenous nicking) retinal changes are reported much more frequently than other subclinical organ damage with documented clinical significance (LVH, carotid plaques and albuminuria), but the prognostic significance of these mild retinal changes has been questioned (119–122) and their reproducibility is limited. These changes appear to be largely nonspecific except for young patients, in whom a deviation from an entirely normal retina should raise concern. More selective methods for objective assessment of the eye fundus have been developed; for example digitalized retinal photographs, which showed that retinal arteriolar and venular narrowing may precede the development of hypertension (123,124).

## BRAIN

Hypertension is associated with an increased risk of ischaemic and haemorrhagic stroke and vascular brain injury (VBI) (125). Brain imaging in hypertension may be used to detect VBI, considered a sign of cerebral small vessel disease (SVD) and an important mediator of the relationship between hypertension and brain ageing. Cerebral SVD

is associated with cognitive, psychiatric and physical disabilities contributing to the risk of stroke, cognitive dysfunction and dementia (126–128). The following signs of VBI can be recognized on brain imaging: white matter hyperintensity, cerebral microbleeds, recent small subcortical infarcts, lacunes, dilated perivascular space and atrophy (129).

Several studies have shown that VBI detected using magnetic resonance imaging (MRI) is quite common in the general population (126,130), with prevalence increasing with age and hypertension. The availability and cost considerations do not allow widespread use of MRI in the evaluation of elderly patients, but silent brain infarcts should be sought in all hypertensives with neural disturbance, and particularly memory loss. Cognitive tests should be used in the clinical assessment of elderly hypertensives (131).

## PROGNOSTIC VALUE OF TREATMENT-INDUCED AND MULTIORGAN SUBCLINICAL ORGAN DAMAGE

Treatment-induced changes in organ damage affect the incidence of CV events, hence organ damage should be assessed also during treatment (132) because LVH regression and reduction of urinary protein excretion indicate treatment-induced CV protection (132,133). There is also some evidence that treatment-induced changes in eGFR predict CV events (134–140).

On the other hand, two meta-analyses did not show any predictive value of treatment-induced reduction in carotid IMT for CV events (141,142). There is no or limited evidence for the predictive power of treatment-induced changes in PWV and ABI.

Whenever possible, a search for subclinical organ damage should be made simultaneously in various organs, because multiorgan subclinical organ damage is associated with a worse prognosis.

A population-based study from Denmark showed that subclinical organ damage predicted CV death independently of SCORE and use of the combination of SCORE and subclinical organ damage may improve risk prediction, particularly in subjects with moderate CV risk, by assessing UAE and PWV (41).

Regression of target-organ damage may not be achieved even under satisfactory BP control. Some changes may be irreversible because they are too advanced. Blood pressure-lowering treatment can also prevent development of target-organ damage (143). If target-organ damage develops during antihypertensive treatment, it may be associated with an increased risk (53).

In conclusion, it is important to assess target-organ damage on treatment; if there is target-organ damage at baseline, its evaluation should be repeated at least once during the first year of effective BP control. If there is no target-organ damage at baseline, the reassessment may be postponed.

## REFERENCES

1. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388: 1659–1724.

2. MacMahon S, Peto R, Cutler J et al. Blood pressure, stroke, and coronary heart disease. Part 1. Prolonged differences in blood pressure: Prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; 335: 765–774.
3. Kannel WB. Blood pressure as a cardiovascular risk factor: Prevention and treatment. *JAMA* 1996; 275: 1571–1576.
4. Assmann G, Schulte H. The Prospective Cardiovascular Munster (PROCAM) study: Prevalence of hyperlipidemia in persons with hypertension and/or diabetes mellitus and the relationship to coronary heart disease. *Am Heart J* 1988; 116: 1713–1724.
5. Walker WG, Neaton JD, Cutler JA et al. Renal function change in hypertensive members of the Multiple Risk Factor Intervention Trial. Racial and treatment effects. The MRFIT Research Group. *JAMA* 1992; 268: 3085–3091.
6. Lloyd-Jones DM, Wang TJ, Leip EP et al. Lifetime risk for development of atrial fibrillation: The Framingham Heart Study. *Circulation* 2004; 110: 1042–1046.
7. Skoog I, Lernfelt B, Landahl S et al. 15-year longitudinal study of blood pressure and dementia. *Lancet* 1996; 347(9009): 1141–1145.
8. Hajjar I, Goldstein FC, Martin GS et al. Roles of arterial stiffness and blood pressure in hypertension-associated cognitive decline in healthy adults. *Hypertension* 2016; 67: 171–175.
9. Lawes CM, Vander Hoorn S, Rodgers A. International Society of Hypertension. Global burden of blood-pressure-related disease, 2001. *Lancet* 2008; 371: 1513–1518.
10. Lewington S, Clarke R, Qizilbash N et al. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360: 1903–1913.
11. Chobanian AV, Bakris GL, Black HR. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003; 42: 1206–1252.
12. Rubinstein A, Colantonio L, Bardach A et al. Estimation of the burden of cardiovascular disease attributable to modifiable risk factors and cost-effectiveness analysis of preventative interventions to reduce this burden in Argentina. *BMC Public Health* 2010; 10: 627.
13. Guidelines Committee 2003. European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; 21: 1011–1053.
14. Mancia G, De Backer G, Dominiczak A et al. 2007 Guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; 25: 1105–1187.
15. Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1281–1357.
16. Whelton PK, Carey RM, Aronow WS et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Hypertension* 2017 November 13. pii: HYP.0000000000000065. doi: 10.1161/HYP.0000000000000065. [Epub ahead of print].
17. Kannel WB. Risk stratification in hypertension: New insights from the Framingham Study. *Am J Hypertens* 2000; 13(Supplement 1): S3–S10.
18. Thomas F, Rudnicki A, Bacri AM et al. Cardiovascular mortality in hypertensive men according to presence of associated risk factors. *Hypertension* 2001; 37: 1256–1261.
19. Wei M, Mitchell BD, Haffner SM et al. Effects of cigarette smoking, diabetes, high cholesterol, and hypertension on all-cause mortality and cardiovascular disease mortality in Mexican Americans. The San Antonio Heart Study. *Am J Epidemiol* 1996; 144: 1058–1065.
20. Assmann G, Schulte H. The Prospective Cardiovascular Münster (PROCAM) study: Prevalence of hyperlipidemia in persons with hypertension and/or diabetes mellitus and the relationship to coronary heart disease. *Am Heart J* 1988; 116(6 Pt 2): 1713–1724.
21. Mancia G, Parati G, Borghi C et al. Hypertension prevalence, awareness, control and association with metabolic abnormalities in the San Marino population: The SMOOTH study. *Hypertens* 2006; 24: 837–843.
22. Mancia G, Facchetti R, Bombelli M et al. Relationship of office, home, and ambulatory blood pressure to blood glucose and lipid variables in the PAMELA population. *Hypertension* 2005; 45: 1072–1077.
23. Asia Pacific Cohort Studies Collaboration. Joint effects of systolic blood pressure and serum cholesterol on cardiovascular disease in the Asia Pacific region. *Circulation* 2005; 112: 3384–3390.
24. Multiple Risk Factor Intervention Trial Research Group. Relationship between baseline risk factors coronary heart disease total mortality in the Multiple risk factor intervention trial. Multiple Risk Factor Intervention Trial Research Group. *Prev Med* 1986; 15: 254–273.
25. Viera AJ, Sheridan SL. Global risk of coronary heart disease: Assessment and application. *Am Fam Physician* 2010; 82: 265–274.
26. Brett T, Arnold-Reed D, Phan C et al. The fremantle primary prevention study: A multicentre randomised trial of absolute cardiovascular risk reduction. *Br J Gen Pract* 2012; 62: e22–e28.
27. Vagholkar S, Zwar N, Jayasinghe UW et al. Influence of cardiovascular absolute risk assessment on prescribing of antihypertensive and lipid-lowering medications: A cluster randomized controlled trial. *Am Heart J* 2014; 167: 28–35.
28. Frikke-Schmidt R, Tybjaerg-Hansen A, Schnohr P et al. Common clinical practice versus new PRIM score in predicting coronary heart disease risk. *Atherosclerosis* 2010; 213: 532–538.
29. Shillinglaw B, Viera AJ, Edwards T et al. Use of global coronary heart disease risk assessment in practice: A cross-sectional survey of a sample of U.S. Physicians. *BMC Health Serv Res* 2012; 12: 20.
30. Anderson KM, Wilson PW, Odell PM et al. An updated coronary risk profile. A Statement for Health Professionals. *Circulation* 1991; 83: 356–362.
31. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106: 3143–3421.
32. Haq IU, Ramsay LE, Yeo WW et al. Is the Framingham risk function valid for northern European populations? A comparison of methods for estimating absolute coronary risk in high risk men. *Heart* 1999; 81: 40–46.
33. Menotti A, Puudu PE, Lanti M. Comparison of the Framingham risk function-based coronary chart with risk function from an Italian population study. *Eur Heart J* 2000; 21: 365–370.
34. Hense HW, Schulte H, Löwel H et al. Framingham risk function overestimates risk of coronary heart disease in men and women from Germany--results from the MONICA Augsburg and the PROCAM cohorts. *Eur Heart J* 2003; 24: 937–945.
35. Goff DC Jr, Lloyd-Jones DM, Bennett G et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; 129: S49–S73.
36. Conroy RM, Pyörälä K, Fitzgerald AP et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: The SCORE project. *Eur Heart J* 2003; 24: 987–1003.
37. Simpson FO. Guidelines for antihypertensive therapy: Problems with a strategy based on absolute cardiovascular risk. *J Hypertens* 1996; 14: 683–689.
38. Zanchetti A. Antihypertensive therapy: How to evaluate the benefits. *Am J Cardiol* 1997; 79: 3–8; discussion 47–48.
39. Cuspidi C, Ambrosioni E, Mancia G et al. Role of echocardiography and carotid ultrasonography in stratifying risk in patients with essential hypertension: The Assessment of Prognostic Risk Observational Survey. *J Hypertens* 2002; 20: 1307–1314.
40. Perk J, De Backer G, Gohlke H et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012; 33: 1635–1701.
41. Sehestedt T, Jeppesen J, Hansen TW et al. Risk prediction is improved by adding markers of subclinical organ damage to SCORE. *Eur Heart J* 2010; 31: 883–891.
42. Sehestedt T, Jeppesen J, Hansen TW et al. Thresholds for pulse wave velocity, urine albumin creatinine ratio and left ventricular mass index using SCORE, Framingham and ESH/ESC risk charts. *J Hypertens* 2012; 30: 1928–1936.
43. Volpe M, Battistoni A, Tocci G et al. Cardiovascular risk assessment beyond systemic coronary risk estimation: A role for organ damage markers. *J Hypertens* 2012; 30: 1056–1064.
44. Levy D, Salomon M, D'Agostino RB, Belanger AJ et al. Prognostic implications of baseline electrocardiographic features and their

- serial changes in subjects with left ventricular hypertrophy. *Circulation* 1994; 90: 1786–1793.
45. Havranek EP, Froshaug DB, Emserman CD et al. Left ventricular hypertrophy and cardiovascular mortality by race and ethnicity. *Am J Med* 2008; 121: 870–875.
  46. Li Z, Dahlöf B, Okin PM et al. Left bundle branch block and cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy: The Losartan Intervention For Endpoint Reduction in Hypertension study. *J Hypertens* 2008; 26: 1244–1249.
  47. Verdecchia P, Angeli F, Cavallini C et al. The voltage of R wave in lead aVL improves risk stratification in hypertensive patients without ECG left ventricular hypertrophy. *J Hypertens* 2009; 27: 1697–1704.
  48. Bacharova L, Schocken D, Estes EH et al. The role of ECG in the diagnosis of left ventricular hypertrophy. *Curr Cardiol Rev* 2014; 10: 257–261.
  49. Okin PM, Devereux RB, Jern S et al. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. *JAMA* 2004; 292: 2343–2349.
  50. Fagard RH, Staessen JA, Thijs L et al. Prognostic significance of electrocardiographic voltages and their serial changes in elderly with systolic hypertension. *Hypertension* 2004; 44: 459–464.
  51. Hancock EW, Deal BJ, Mirvis DM et al. AHA/ACC/HRS recommendations for the standardization and interpretation of the electrocardiogram: Part V: Electrocardiogram changes associated with cardiac chamber hypertrophy: A scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol* 2009; 53: 992–1002.
  52. Okin PM, Oikarinen L, Viitasalo M et al. Prognostic value of changes in the electrocardiographic strain pattern during antihypertensive treatment: The Losartan Intervention For End-Point Reduction in Hypertension Study (LIFE). *Circulation* 2009; 119: 1883–1891.
  53. Izzo R, Losi MA, Stabile E et al. Development of left ventricular hypertrophy in treated hypertensive outpatients: The Campania Salute network. *Hypertension* 2017; 69: 136–142.
  54. Morin DP, Oikarinen L, Viitasalo M et al. QRS duration predicts sudden cardiac death in hypertensive patients undergoing intensive medical therapy: The LIFE study. *Eur Heart J* 2009; 30: 2908–2914.
  55. Wachtell K, Horneftam B, Lehto M et al. Cardiovascular morbidity and mortality in hypertensive patients with a history of atrial fibrillation: The Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. *J Am Coll Cardiol* 2005; 45: 705–711.
  56. Chrispin J, Jain A, Soliman EZ et al. Association of electrocardiographic and imaging surrogates of left ventricular hypertrophy with incident atrial fibrillation: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2014; 63: 2007–2013.
  57. Reichel N, Devereux RB. Left ventricular hypertrophy: Relationship of anatomic, echocardiographic and electrocardiographic findings. *Circulation* 1981; 63: 1391–1398.
  58. Levy D, Garrison RJ, Savage DD et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990; 322: 1561–1566.
  59. Tsioufis C, Kokkinos P, Macmanus C et al. Left ventricular hypertrophy as a determinant of renal outcome in patients with high cardiovascular risk. *J Hypertens* 2010; 28: 2299–2308.
  60. Lang RM, Bierig M, Devereux RB et al. Recommendations for chamber quantification. *Eur J Echocardiogr* 2006; 7: 79–108.
  61. Koren MJ, Devereux RB, Casale PN et al. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991; 114: 345–352.
  62. Verdecchia P, Schillaci G, Borgioni C et al. Adverse prognostic significance of concentric remodeling of the left ventricle in hypertensive patients with normal left ventricular mass. *J Am Coll Cardiol* 1995; 25: 871–878.
  63. Muiesan ML, Salvetti M, Monteduro C et al. Left ventricular concentric geometry during treatment adversely affects cardiovascular prognosis in hypertensive patients. *Hypertension* 2004; 43: 731–738.
  64. Zanchetti A, Cuspidi C, Comarella L et al. Left ventricular diastolic dysfunction in elderly hypertensives: Results of the APROS-diadys study. *J Hypertens* 2007; 25: 2158–2167.
  65. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function: Epidemiology, clinical characteristics and prognosis. *J Am Coll Cardiol* 2004; 43: 317–327.
  66. Tsang TS, Barnes ME, Gersh BJ et al. Risks for atrial fibrillation and congestive heart failure in patients  $\geq 65$  years of age with abnormal left ventricular diastolic relaxation. *Am J Cardiol* 2004; 93: 54–58.
  67. Aurigemma GP, Gottdiener JS, Shemanski L et al. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: The cardiovascular health study. *J Am Coll Cardiol* 2001; 37: 1042–1048.
  68. Redfield MM, Jacobsen SJ, Burnett JC Jr et al. Burden of systolic and diastolic ventricular dysfunction in the community: Appreciating the scope of the heart failure epidemic. *JAMA* 2003; 289: 194–202.
  69. Bella JN, Palmieri V, Roman MJ et al. Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults: The Strong Heart Study. *Circulation* 2002; 105: 1928–1933.
  70. Laukkanen JA, Kurl S, Eränen J et al. Left atrium size and the risk of cardiovascular death in middle-aged men. *Arch Intern Med* 2005; 165: 1788–1793.
  71. Verdecchia P, Reboldi G, Gattobigio R et al. Atrial fibrillation in hypertension: Predictors and outcome. *Hypertension* 2003; 41: 218–223.
  72. Kizer JR, Bella JN, Palmieri V et al. Left atrial diameter as an independent predictor of first clinical cardiovascular events in middle-aged and elderly adults: The Strong Heart Study (SHS). *Am Heart J* 2006; 151: 412–418.
  73. Abhayaratna WP, Seward JB, Appleton CP et al. Left atrial size: Physiologic determinants and clinical applications. *J Am Coll Cardiol* 2006; 47: 2357–2363.
  74. Takeuchi M, Nishikage T, Mor-Avi V et al. Measurement of left ventricular mass by real-time three-dimensional echocardiography: Validation against magnetic resonance and comparison with two-dimensional and m-mode measurements. *J Am Soc Echocardiogr* 2008; 21: 1001–1005.
  75. Bots ML, Hoes AW, Koudstaal PJ et al. Common carotid intima-media thickness and risk of stroke and myocardial infarction: The Rotterdam Study. *Circulation* 1997; 96: 1432–1437.
  76. Hodis HN, Mack WJ, LaBree L et al. The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med* 1998; 128: 262–269.
  77. Vlachopoulos C, Xaplanteris P, Aboyans V et al. The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: Endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. *Atherosclerosis* 2015; 241: 507–532.
  78. Zanchetti A, Bond MG, Hennig M et al. Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: Principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. *Circulation* 2002; 106: 2422–2427.
  79. Zanchetti A, Bond MG, Hennig M et al. Absolute and relative changes in carotid intima-media thickness and atherosclerotic plaques during long-term antihypertensive treatment: Further results of the European Lacidipine Study on Atherosclerosis (ELSA). *J Hypertens* 2004; 22: 1201–1212.
  80. Zanchetti A, Rosei EA, Dal Palù C et al. The Verapamil in Hypertension and Atherosclerosis Study (VHAS): Results of long-term randomized treatment with either verapamil or chlorthalidone on carotid intima-media thickness. *J Hypertens* 1998; 16: 1667–1676.
  81. Zanchetti A, Hennig M, Hollweck R et al. Baseline values but not treatment-induced changes in carotid intima-media thickness predict incident cardiovascular events in treated hypertensive patients: Findings in the European Lacidipine Study on Atherosclerosis (ELSA). *Circulation* 2009; 120: 1084–1090.
  82. Den Ruijter HM, Peters SA, Anderson TJ et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: A meta-analysis. *JAMA* 2012; 308: 796–803.
  83. Piepoli MF, Hoes AW, Agewall S et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016; 37: 2315–2381.
  84. Sehestedt T, Jeppesen J, Hansen TW et al. Which markers of subclinical organ damage to measure in individuals with high normal blood pressure? *J Hypertens* 2009; 27: 1165–1171.



85. Criqui MH, Langer RD, Fronek A et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992; 326: 381–386.
86. Fowkes FG, Murray GD, Newman AB et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: A meta-analysis. *JAMA* 2008; 300: 197–208.
87. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med* 2001; 344: 1608–1621.
88. Vogt MT, Cauley JA, Newman AB et al. Decreased ankle/arm blood pressure index and mortality in elderly women. *JAMA* 1993; 270: 465–469.
89. McKenna M, Wolfson S, Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. *Atherosclerosis* 1991; 87: 119–128.
90. Vogt MT, McKenna M, Anderson SJ et al. The relationship between ankle-arm index and mortality in older men and women. *J Am Geriatr Soc* 1993; 41: 523–530.
91. Burek KA, Sutton-Tyrrell K, Brooks MM et al. Prognostic importance of lower extremity arterial disease in patients undergoing coronary revascularization in the Bypass Angioplasty Revascularization Investigation (BARI). *J Am Coll Cardiol* 1999; 34: 716–721.
92. Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation* 2003; 107: 2864–2869.
93. Laurent S, Cockcroft J, Van Bortel L et al. Expert consensus document on arterial stiffness: Methodological issues and clinical applications. *Eur Heart J* 2006; 27: 2588–2605.
94. Willum-Hansen T, Staessen JA, Torp-Pedersen C et al. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation* 2006; 113: 664–670.
95. Laurent S, Boutouyrie P, Asmar R et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; 37: 1236–1241.
96. Laurent S, Katsahian S, Fassot C et al. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. *Stroke* 2003; 34: 1203–1206.
97. Boutouyrie P, Tropeano AI, Asmar R et al. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: A longitudinal study. *Hypertension* 2002; 39: 10–15.
98. Ben-Shlomo Y, Spears M, Boustred C et al. Aortic pulse wave velocity improves cardiovascular event prediction: An individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol* 2014; 63: 636–646.
99. Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J* 2010; 31: 2338–2350.
100. Van Bortel LM, Laurent S, Boutouyrie P et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens* 2012; 30: 445–448.
101. Jankowski P, Kawecka-Jaszcz K, Czarnecka D et al. Pulsatile but not steady component of blood pressure predicts cardiovascular events in coronary patients. *Hypertension* 2008; 51: 848–855.
102. Wang KL, Cheng HM, Chuang SY et al. Central or peripheral systolic or pulse pressure: Which best relates to target organs and future mortality? *J Hypertens* 2009; 27: 461–467.
103. Williams B, Lacy PS, Thom SM et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: Principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006; 113: 1213–1225.
104. Sharman JE, Marwick TH, Gilroy D et al. Randomized trial of guiding hypertension management using central aortic blood pressure compared with best practice care: Principal findings of the BP GUIDE study. *Hypertension* 2013; 62: 1138–1145.
105. Stevens LA, Coresh J, Greene T et al. Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med* 2006; 354: 2473–2483.
106. Levey AS, Stevens LA, Schmid CH et al. CKD EPI. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612.
107. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; 3: 1–150.
108. Shlipak MG, Katz R, Sarnak MJ et al. Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. *Ann Intern Med* 2006; 145: 237–246.
109. Parving HH. Initiation and progression of diabetic nephropathy. *N Engl J Med* 1996; 335: 1682–1683.
110. Ravid LM, Rodicio JL. Clinical relevance of proteinuria and microalbuminuria. *Curr Opin Nephrol Hypertens* 1993; 2: 962–967.
111. Redon J, Williams B. Microalbuminuria in essential hypertension: Redefining the threshold. *J Hypertens* 2002; 20: 353–355.
112. Arnlöv J, Evans JC, Meigs JB et al. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: The Framingham Heart Study. *Circulation* 2005; 112: 969–975.
113. Hillege HL, Fidler V, Diercks GF et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002; 106: 1777–1782.
114. National Kidney Foundation. Executive Summary. *Am J Kid Dis* 2004; 43(Suppl 1): S16–S33.
115. Gerstein HC, Mann JF, Yi Q et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; 286: 421–426.
116. Mallat SG, Al Kattar S, Tanios BY et al. Hyperuricemia, hypertension, and chronic kidney disease: An emerging association. *Curr Hypertens Rep* 2016; 18: 74–76.
117. Wong TY, Klein R, Sharrett AR et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. *JAMA* 2002; 287: 1153–1159.
118. Wong TY, Klein R, Couper DJ et al. Retinal microvascular abnormalities and incident stroke: The Atherosclerosis Risk in Communities Study. *Lancet* 2001; 358: 1134–1140.
119. Cuspidi C, Macca G, Salerno M et al. Evaluation of target organ damage in arterial hypertension: Which role for qualitative fundoscopic examination? *Ital Heart J* 2001; 2: 702–706.
120. Dimmitt SB, West JN, Eames SM et al. Usefulness of ophthalmoscopy in mild to moderate hypertension. *Lancet* 1989; 20: 1103–1106.
121. Fuchs FD, Maestri MK, Bredemeier M et al. Study of the usefulness of optic fundi examination of patients with hypertension in a clinical setting. *J Hum Hypertens* 1995; 9: 547–551.
122. Sairenchi T, Iso H, Yamagishi K et al. Mild retinopathy is a risk factor for cardiovascular mortality in Japanese with and without hypertension: The Ibaraki Prefectural Health Study. *Circulation* 2011; 124: 2502–2511.
123. Antonios TF, Singer DR, Markandu ND et al. Rarefaction of skin capillaries in borderline essential hypertension suggests an early structural abnormality. *Hypertension* 1999; 34: 655–658.
124. Noon JP, Walker BR, Webb DJ et al. Impaired microvascular dilatation and capillary rarefaction in young adults with a predisposition to high blood pressure. *J Clin Invest* 1997; 99: 1873–1879.
125. Henskens LH, van Oostenbrugge RJ, Kroon AA et al. Detection of silent cerebrovascular disease refines risk stratification of hypertensive patients. *J Hypertens* 2009; 27(4): 846–853.
126. Longstreth WT Jr, Manolio TA, Arnold A et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke* 1996; 27: 1274–1282.
127. Prins ND, van Dijk EJ, den Heijer T et al. Cerebral white matter lesions and the risk of dementia. *Arch Neurol* 2004; 61: 1531–154.
128. Vermeer SE, Hollander M, van Dijk EJ et al. Silent brain infarcts and white matter lesions increase stroke risk in the general population: The Rotterdam Scan Study. *Stroke* 2003; 34: 1126–1129.
129. Wardlaw JM, Smith EE, Biessels GJ et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013; 12(8): 822–838.
130. Vermeer SE, Koudstaal PJ, Oudkerk M et al. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. *Stroke* 2002; 33: 21–25.
131. Tsoi KK, Chan JY, Hirai HW et al. Cognitive tests to detect dementia: A systematic review and meta-analysis. *JAMA Intern Med* 2015; 175: 1450–1458.
132. Devereux RB, Wachtell K, Gerds E et al. Prognostic significance of left ventricular mass change during treatment of hypertension. *JAMA* 2004; 292: 2350–2356.
133. Ibsen H, Olsen MH, Wachtell K et al. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: Losartan intervention for endpoint reduction in hypertension study. *Hypertension* 2005; 45: 198–202.
134. Inker LA, Levey AS, Pandya K et al. Early change in proteinuria as a surrogate end point for kidney disease progression: An individual patient meta-analysis. *Am J Kidney Dis* 2014; 64: 74–85.

135. Bakris GL, Sarafidis PA, Weir MR et al. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): A prespecified secondary analysis of a randomised controlled trial. *Lancet* 2010; 375: 1173–1181.
136. Haller H, Ito S, Izzo JL Jr et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med* 2011; 364: 907–917.
137. Holtkamp FA, de Zeeuw D, de Graeff PA et al. Albuminuria and blood pressure, independent targets for cardioprotective therapy in patients with diabetes and nephropathy: A post hoc analysis of the combined RENAAL and IDNT trials. *Eur Heart J* 2011; 32: 1493–1499.
138. Drawz PE, Rosenberg ME. Slowing progression of chronic kidney disease. *Kidney Int Suppl (2011)*. 2013; 3: 372–376.
139. de Galan BE, Perkovic V, Ninomiya T et al. Lowering blood pressure reduces renal events in type 2 diabetes. *J Am Soc Nephrol* 2009; 20: 883–892.
140. Ninomiya T, Perkovic V, de Galan BE et al. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. *J Am Soc Nephrol* 2009; 20: 1813–1821.
141. Costanzo P, Perrone-Filardi P, Vassallo E et al. Does carotid intima-media thickness regression predict reduction of cardiovascular events? A meta-analysis of 41 randomized trials. *J Am Coll Cardiol* 2010; 56: 2006–2020.
142. Wang JG, Staessen JA, Li Y et al. Carotid intima-media thickness and antihypertensive treatment: A meta-analysis of randomized controlled trials. *Stroke* 2006; 37: 1933–1940.
143. Verdecchia P, Sleight P, Mancia G et al. Effects of telmisartan, ramipril, and their combination on left ventricular hypertrophy in individuals at high vascular risk in the ongoing telmisartan alone and in combination with Ramipril global end point trial and the telmisartan randomized assessment study in ACE intolerant subjects with cardiovascular disease. *Circulation* 2009; 120: 1380–1389.



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# HYPERTENSION AND THE KIDNEY

# 3

*Roberto Pontremoli, Giovanna Leoncini and Francesca Viazzi*

Hypertension and kidney share a bidirectional relationship. The kidneys participate in the development and maintenance of primary hypertension and chronic kidney disease (CKD) is one of the most common causes of secondary hypertension. On the other hand, increased blood pressure of any etiology can lead to renal damage and, especially if accompanied by proteinuria, is an important factor for CKD progression.

## **HYPERTENSION, CHRONIC KIDNEY DISEASE AND CARDIOVASCULAR RISK**

Primary hypertension was present in only 5–10% of the adult population in the early 1900s, but over the last several decades its prevalence has steadily increased to the remarkable figure of 30–40% currently reported in most developed countries. It is projected that there will be more than 1.5 billion people affected by hypertension worldwide by the year 2025 (1). Based on surveys conducted in the 1990s, Europe should be considered as a region with high hypertension prevalence as compared to the United States and Canada (2). Furthermore, most recent epidemiological studies (3) indicate the highest prevalence of hypertension in Central and Eastern European countries and the lowest in northern and southern countries, ranging between 32% (Estonia) and 15% (UK).

Approximately 10% of the population worldwide is affected by chronic kidney disease (CKD) with significant differences among regions. While increasing life expectancy has an impact on CKD, as ageing is traditionally associated with a loss of renal function, nonetheless recent demographic trends alone cannot explain the steep increase in the prevalence and incidence of CKD recently recorded. The rising prevalence of several well-known risk factors for renal damage such as diabetes mellitus, hypertension, smoking and obesity as well as public health policies may affect CKD prevalence. Data from the 2013 ERA-EDTA Registry Annual Report (4) indicate that the number of patients starting renal replacement therapy (RRT) varies considerably from less than 30 to over 200 people per million population across European countries, with higher prevalence in high income countries

and a significant heterogeneity among regions, from 3.3% in Norway to 17.3% in northeast Germany. Even when restricting the analysis to more severe stages, and accounting for stratification by risk factors such as diabetes, hypertension and obesity in the general population, differences among regions remain substantial: prevalence of CKD stages 3–5 varies from 1.0% in Italy to 5.9% in northeast Germany (5).

CKD is frequently observed in patients with arterial hypertension, as the same factors that promote the development and progression of atherosclerosis can also promote CKD. Assessment of hypertension-related kidney damage requires the evaluation of glomerular filtration rate (GFR) as well as quantification of albuminuria. Knowledge of both these markers allows renal and cardiovascular risk assessment at the same time (6). The coexistence of CKD in hypertension is accompanied by a further significant enhancement in CV risk that reinforces the need for simultaneous protection of both the renal and the CV systems.

While hypertension is a well-known and strong risk factor for development of CKD, the latter, even in its early phases, can cause an increase in blood pressure, thereby contributing to increase cardiovascular risk in affected patients (7). An inverse relationship between renal functional impairment and prevalence of hypertension has been reported in the Chronic Renal Insufficiency Cohort (CRIC) study in which about 92% of patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m<sup>2</sup> were hypertensive, while 67% of those with eGFR >60 mL/min/1.73 m<sup>2</sup> had elevated blood pressure (BP) (8). The prevalence of hypertension in CKD seems also to depend on the type of nephropathy, being highest in renal vascular disease (93%), in established diabetic nephropathy (87%) and in polycystic kidney disease (74%) compared to a lower prevalence in glomerulonephritis and tubular interstitial disease (9). Furthermore, clinic blood pressure measurements might be misleading, since masked hypertension may occur in up to 30% and apparent treatment-resistant hypertension in up to 40% of patients with CKD (10).

Unsurprisingly, it has recently been emphasized that renal impairment is also the most common cause of treatment-resistant hypertension, defined as the failure to achieve recommended BP values despite an optimal combination of at least three different drugs, including a diuretic (11).



## THE KIDNEY IN PRIMARY HYPERTENSION

Since the seminal experimental work by Guyton and Laragh in the 1960s and 1970s, an impaired ability of the kidney to excrete sodium in response to elevated BP has been regarded as a major contributor to hypertension, irrespective of the initiating cause (12). More recent work suggests that novel mechanisms controlling key sodium transporters within the kidney have a critical influence on the development and maintenance of hypertension. Thus, impaired renal sodium excretion may be looked at as the final common pathway through which vascular, neural and inflammatory abnormalities contribute to blood pressure elevation. A more in-depth understanding of the role of the kidney as both a cause and target of hypertension may lead to identification of new, more effective preventive and therapeutic strategies.

**Hypertension and cardio-renal interaction.** The idea that the kidney plays a role in hypertension dates back almost 200 years. In the nineteenth century, Richard Bright, reporting on a series of careful postmortem examinations, first noted an intriguing association between enlarged heart chambers and shrunken kidneys, even in the absence of pathologic changes in cardiac valves. These findings we can now attribute to the presence of hypertensive-mediated left ventricular hypertrophy in the context of CKD may signal the first scientific reference to a clinical-pathologic cardio-renal interaction (13).

**The kidney as the long-term regulator of BP and fluid homeostasis.** In the 1970s, Arthur Guyton and colleagues provided solid experimental and clinical evidence in support of the dominant role of the kidney in the regulation of BP through its long-term fine tuning of extracellular fluid volume. Building on the hypothesis that the maintenance of body fluid balance requires an accurate match between salt and water intake and output (14), Guyton elegantly showed that any increase in BP, independent of its cause, will eventually be reverted in the long run by the consequent increase in renal perfusion pressure, a phenomenon called pressure-natriuresis (Figure 3.1). This mechanism was proved to have sufficient gain to limit intravascular volume expansion and to lower blood pressure in response to a wide range of stimuli such as increase in heart rate or elevated peripheral vascular resistance (15,16). According to Guyton's experimental work, a modification of the pressure-natriuresis response with a shift to a higher BP level is a prerequisite in order to produce a sustained, long-term BP elevation at the systemic level. However, more recent evidence points toward a more complex relationship between sodium retention and extracellular fluid volume homeostasis.

**Hypertension follows the kidney.** In more recent years, a series of elegant experimental studies on kidney cross-transplantation has provided further evidence of an intrinsic role of the kidney in the pathogenesis of hypertension (17–20). Using genetically compatible donor and recipient strains of rats, these studies showed that 'hypertension follows the kidney'. In fact, transplanting the kidneys of hypertension-prone rats into normotensive strains after both native kidneys had been removed was able to induce the development of hypertension. Conversely, transplanting a kidney from a normotensive salt-resistant strain into a salt-sensitive, hypertension-prone animal abrogated hypertension (20). This proof of concept was later confirmed to a certain extent in

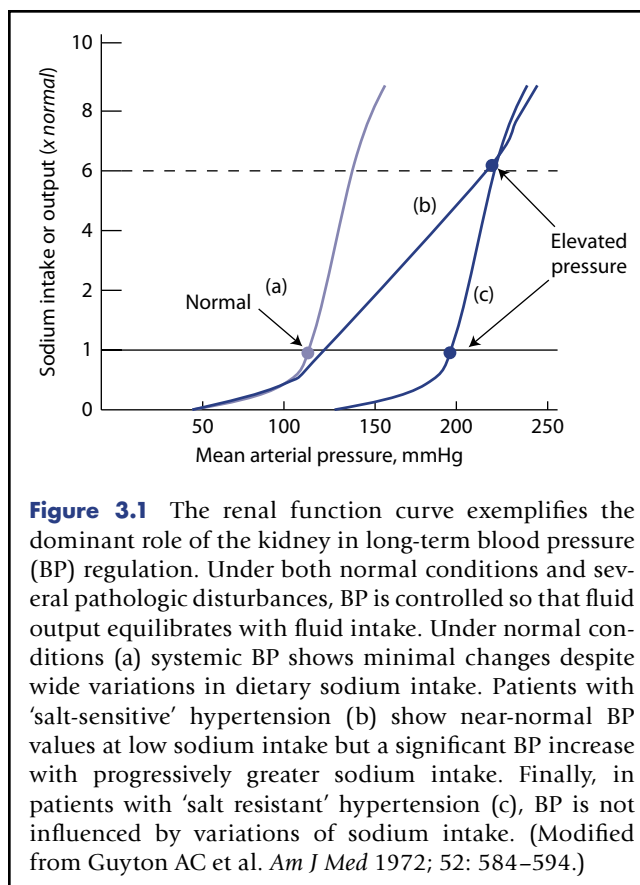


**Figure 3.1** The renal function curve exemplifies the dominant role of the kidney in long-term blood pressure (BP) regulation. Under both normal conditions and several pathologic disturbances, BP is controlled so that fluid output equilibrates with fluid intake. Under normal conditions (a) systemic BP shows minimal changes despite wide variations in dietary sodium intake. Patients with 'salt-sensitive' hypertension (b) show near-normal BP values at low sodium intake but a significant BP increase with progressively greater sodium intake. Finally, in patients with 'salt resistant' hypertension (c), BP is not influenced by variations of sodium intake. (Modified from Guyton AC et al. *Am J Med* 1972; 52: 584–594.)

humans by showing that regaining a considerable degree of renal function after successful renal transplantation was associated with an improvement of blood pressure control in resistant hypertension (21). Altogether these studies support a pivotal role of the kidney and its control over sodium balance on blood pressure homeostasis and the susceptibility to develop hypertension.

**Renin-angiotensin-aldosterone system (RAAS) and BP.** The RAAS has long been regarded as a major contributor to BP homeostasis, and its hyperactivity leads to hypertension development (Figure 3.2). Accordingly, the use of drugs which interfere with the activity of the RAAS has been shown to effectively lower BP (22), confirming a role of this hormonal system in the genesis of high BP (23). In particular, angiotensin II, the final effector of the enzymatic cascade, was shown to influence BP regulation by modulating pressure natriuresis relationship through its action at different sites within the nephron (24) (Figure 3.3). Furthermore, several lines of evidence suggest that the RAAS may also act as an intra-renal paracrine system influencing BP regulation and sodium homeostasis even independently of systemic RAAS (25).

**New models of sodium homeostasis.** On the other hand, recent innovative studies by Titze and associates indicate that total-body sodium handling is more complex than the classical two-compartment Guytonian model, which postulates that changes in BP are associated and secondary to sodium retention and blood volume expansion (26). According to these groundbreaking studies, sodium may accumulate in the subdermal interstitium at hypertonic concentrations in complexes with proteoglycans (27), triggering the infiltration of macrophages and ultimately promoting production of vascular endothelial growth factor-C (VEGF-C) (26), a potent

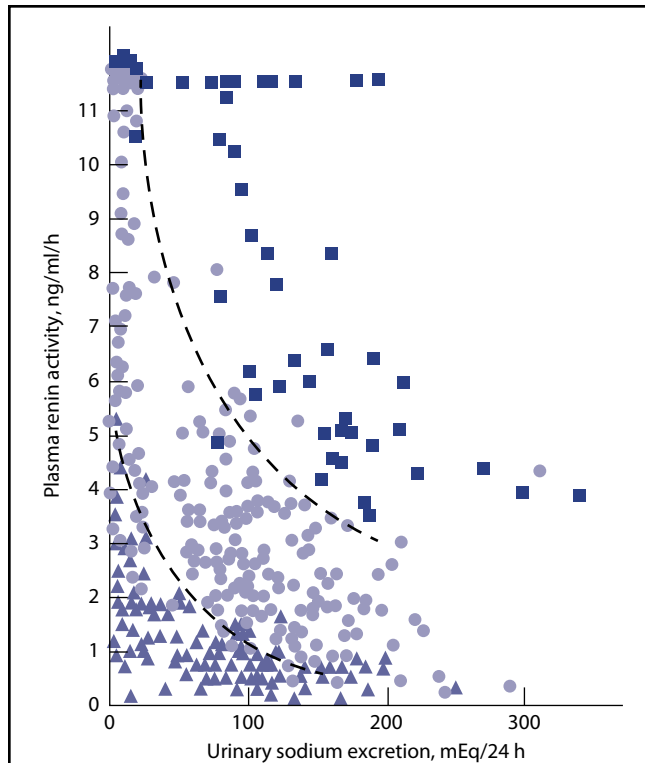


**Figure 3.2** The renin–angiotensin–aldosterone system has long been regarded as a major contributor to BP homeostasis and its hyperactivity leads to hypertension development. Plasma renin varies according to changes in sodium balance in primary hypertension. (Modified from Laragh JH, Sealey J, Brunner HR. *Am J Med.* 1972 Nov;53(5):649–63.)

inducer of lymphangiogenesis. Indeed, preclinical studies predict that reduced levels of VEGF-C may promote hypertension. Consistent with this hypothesis, a recent report showed that overexpression of VEGF-C lowered blood pressure, opening the way to clarification of novel mechanistic pathways and therapeutic targets.

**Immune mechanisms in hypertension.** Recent experimental evidence suggests that BP control may also be influenced by immune mechanisms, mainly through cellular and humoral modulation of inflammatory processes acting within the kidney. This is supported by clinical studies showing that immunosuppressive treatment lowers blood pressure in hypertensive patients with rheumatologic disorders (28). Furthermore, activation of the NF- $\kappa$ B inflammatory pathway within the central nervous system potentiates sympathetic outflow (29–31), thereby stimulating sodium retention at the renal level. In addition, studies conducted on gene-knockout animals support a role for inflammatory cytokines on BP regulation and end-organ damage development.

Several other pathogenetic mechanisms contribute to the tightly interwoven relationship between the kidney and hypertension. *Sympathetic nervous system activation*, manifested by increases in systemic catecholamine levels, leads to vasoconstriction, endothelial dysfunction and a salt-avid state (32,33). Recent evidence also indicates that in the earlier clinical phases of kidney disease, sympathetic activation is detectable. Further data show that

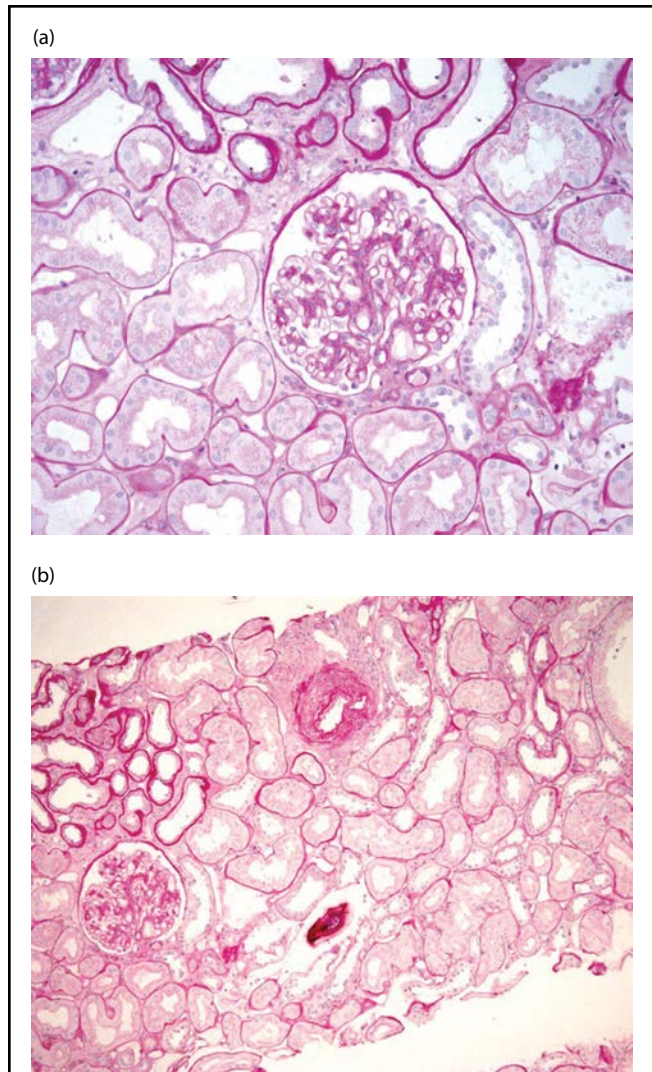


**Figure 3.3** (a) Benign nephrosclerosis is characterized by progressive thickening and sclerosis of the renal vessels, with a substantial sparing of glomerular capillaries (PAS). (b) Hypertension-mediated renal damage in early stages of diabetic nephropathy is predominantly glomerular, with a pattern of incipient segmental or global glomerulosclerosis (PAS). (Courtesy of Dr. B. Villaggio.)

sympathetic neural mechanisms participate in renal and/or hypertensive disease progression, favouring the development of target-organ damage. Finally, recent findings indicate that the metabolic disarray frequently complicating the high blood pressure state (metabolic syndrome, dyslipidemia, insulin resistance) may have as pathophysiological background a sympathetic overdrive (34).

At the level of the *endothelium*, the interplay of nitric oxide, endothelin-1 and oxidative stress figure prominently in BP homeostasis. Endothelial production of the vasoactive peptide nitric oxide results in vascular smooth muscle relaxation, a process stimulated by flow (i.e. blood pressure)-induced shear stress (35). Oxide-mediated vasodilation is counteracted by endothelin-1, a vasoconstricting substance whose production is enhanced by activation during renal damage of the aforementioned RAAS and

sympathetic nervous systems. Further attenuating hypotensive effect of nitric oxide is the generation of reactive oxygen species by catecholamines, vascular distention and RAAS activation. These free radicals are both proinflammatory and decrease nitric oxide bioavailability, ultimately promoting increases in BP (36).

*Arterial stiffness*, long considered a consequence of hypertension, may indeed antecede its onset. For example, owing to the pulsatile load associated with ventricular contraction, arteriolar elastin fibres are fractured and ultimately replaced by the less distensible collagen, further decreasing vascular compliance (37).

*Serum uric acid (SUA)* is both a product of purine degradation and a result of renal handling, therefore largely dependent on renal function. A great deal of experimental and clinical evidence supports the possibility that an elevated SUA level may independently lead to or worsen hypertension. The mechanisms linking hyperuricemia to hypertension remain uncertain at present, and include endothelial dysfunction and arterial stiffening through increased oxidative stress, RAAS activity and inflammation (38,39).

## THE KIDNEY AS A VICTIM OF HYPERTENSION

The kidney is a major target for hypertensive organ damage. Data from several renal databases identifies systemic hypertension as the second most common cause of end-stage renal disease (ESRD), with diabetic nephropathy being the first. In the United States, hypertension is the leading cause of ESRD in African American patients. In Europe, according to 2015 ERA-EDTA registry (40), hypertensive nephrosclerosis is a less common cause of ESRD, accounting for 14% of new patients starting RRT. However, the incidence varies among countries – hypertensive nephrosclerosis is reported as responsible for ESRD in 25% and 29% in patients starting RRT in France and in Norway, while in the UK this figure is approximately 6%.

Most hypertensive patients develop mild to moderate hypertensive nephrosclerosis that progresses to ESRD in only a relatively small percentage of patients. In particular, elevations in serum creatinine have not been frequently observed in clinical trials involving patients of European ancestry with mild-to-moderate hypertension. Defining CKD as a rise in baseline serum creatinine concentration by 50% or to levels  $>2$  mg/dL, the disease was detected in 0.1% (approximately 1 per 1000) of participants with mild-to-moderate hypertension in the Multiple Risk Factor Intervention Trial (MRFIT) (41). On the contrary, in the Hypertension Detection and Follow-up Program (HDFP) which enrolled a relatively large percentage of African American subjects, 1% of participants developed an elevated serum creatinine concentration, which probably reflects the role of increased genetic susceptibility to nondiabetic nephropathy in this ethnicity (42).

The lack of specific criteria to define a histological diagnosis often limits a clear demonstration that hypertension causes the development of renal damage and makes it difficult to correctly estimate the impact of hypertension in renal dysfunction. In fact, regardless of the underlying etiology of CKD, the increase in systemic blood pressure accelerates per se the rate of glomerular filtration rate deterioration, especially in the presence of proteinuria. However, many aspects of hypertension-related renal

damage, such as the individual susceptibility to hypertensive renal damage and the different renoprotective effect of various antihypertensive drug classes, are still incompletely understood (43). The renal pathology typically observed in the vast majority of individuals with primary hypertension is benign nephrosclerosis, a condition characterized by accelerated ageing of the renal vasculature with a slow progressive thickening and sclerosis of the renal resistance vessels, with a substantial sparing of glomerular capillaries (Figure 3.3a). Therefore, it is not surprising that primary hypertension rarely leads to advanced stages of renal damage. In fact, except for genetically susceptible groups, such as blacks, the only individuals with primary hypertension who develop severe hypertension-induced renal damage to reach ESRD are those with very high levels of BP that result in the development of malignant nephrosclerosis, characterized by acute disruptive injury and fibrinoid necrosis of small arteries, arterioles and glomerular capillaries, with a prevalent glomerular ischemia. In these cases, acute renal failure develops over days, and despite treatment is often followed by progressive renal damage leading to CKD or even ESRD.

On the other hand, individuals with CKD and diabetes seem to have greater susceptibility to the adverse renal effects of even moderate hypertension. At variance with the largely vascular pathology of benign and malignant nephrosclerosis, the site of hypertension-related renal damage in CKD is predominantly glomerular, with a pattern of accelerated segmental or global glomerulosclerosis often superimposed on the intrinsic phenotype peculiar of the underlying renal disease (Figure 3.3b). Recent studies have hypothesized that the severity of such damage depends on the degree to which renal autoregulatory mechanisms fail to prevent the transmission of BP elevation to renal microvasculature. In fact, under normal physiologic conditions, autoregulatory vasoconstriction of the preglomerular resistance vessels, mainly the afferent arteriole, prevents transmission of systemic hypertension to glomerular microvasculature, thus maintaining constant renal blood flow, intraglomerular hydrostatic pressure and ultimately preserving GFR and avoiding hypertensive renal damage. In patients with chronic hypertension, both upper and lower thresholds of autoregulation are usually shifted to the right as a means of protective adaptation. However, intrarenal resistance arteries and arterioles exposed to long-term hemodynamic stress progressively develop atherosclerotic changes leading to benign nephrosclerosis. Furthermore, an acute and severe increase in BP is probably able to exceed the autoregulatory limits and may cause more disruptive vascular damage particular to malignant nephrosclerosis. An impairment of these protective mechanisms associated with a significant reduction in renal mass in patients with diabetic and nondiabetic CKD is likely to account for their increased susceptibility to progressive glomerulosclerosis even with a moderate increase in systemic BP. In addition, the consequent renal damage results in additional nephron loss and further strengthens transmission of systemic hemodynamic load to the glomerulus.

## CONCLUSIONS

The kidney presides over long-term extracellular fluid and BP homeostasis by balancing dietary sodium intake and



excretion in the urine. This is the result of a complex physiological interaction among hormones, inflammatory mediators, and the sympathetic nervous system. It is evident that a basic mechanism of efficacy for diuretics and dietary sodium restriction in hypertension is to favourably influence sodium balance and homeostasis. Dietary sodium restriction as well as many antihypertensive agents exert their BP reduction activity by facilitating pressure-natriuresis. Recent studies suggest that pathways regulating extrarenal sodium disposition might also be useful targets for enhancing elimination of sodium and reducing BP in hypertension. The bidirectional relationship between the kidney and high BP is further proved by the well-known exceedingly high prevalence of hypertension in patients with CKD, wherein effective antihypertensive treatment is able to convey the dual benefit of renal and cardiovascular risk reduction.

## REFERENCES

- Kearney PM, Whelton M, Reynolds K et al. Global burden of hypertension: Analysis of worldwide data. *Lancet* 2005; 365: 217–223.
- Wolf-Maier K, Wolf-Maier K, Cooper RS, Banegas JR et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA* 2003; 289: 2363–2369.
- Wilkins E, Wilson L, Wickramasinghe K et al. *European Cardiovascular Disease Statistics 2017*. European Heart Network, Brussels; 2017. Available at: <http://www.ehnheart.org/images/CVD-statistics-report-August-2017.pdf> (accessed 17 December 2017).
- Kramer A, Pippas M, Stel VS et al. Renal replacement therapy in Europe: A summary of the 2013 ERA-EDTA Registry Annual Report with a focus on diabetes mellitus. *Clin Kidney J* 2016; 9: 457–469.
- Brück K, Stel VS, Gambaro G et al. European CKD Burden Consortium. CKD prevalence varies across the European general population. *J Am Soc Nephrol* 2016; 27: 2135–2147.
- Mancia G, Fagard R, Narkiewicz K et al. Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1281–1357.
- Whelton PK, Carey RM, Aronow WS et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2017 November 13. [Epub ahead of print].
- Muntner P, Anderson A, Charleston J et al. Hypertension awareness, treatment and control in adults with chronic kidney disease: Results from the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis* 2010; 55: 441–451.
- Ridao N, Luno J, De Vinuesa SG et al. Prevalence of hypertension in renal disease. *Nephrol Dial Transplant* 2001; 16: 70–73.
- Thomas G, Xie D, Chen HY et al. CRIC Study Investigators. Prevalence and prognostic significance of apparent treatment resistant hypertension in chronic kidney disease: Report from the chronic renal insufficiency cohort study. *Hypertension* 2016; 67: 387–396.
- Rosignol P, Massy ZA, Azizi M et al. ERA-EDTA EURECA-m working group. Red de Investigación Renal (REDINREN) network: Cardiovascular and Renal Clinical Trialists (F-CRIN INI-CRCT) network. The double challenge of resistant hypertension and chronic kidney disease. *Lancet* 2015; 386: 1588–1598.
- Coffman TM. The inextricable role of the kidney in hypertension. *J Clin Invest* 2014; 124: 2341–2347.
- Bright R. Observations on the treatment of fever. Case of simple fever, protracted by irritation of the bowels, and attended by relapse. In: *Guy's Hospital Reports. Vol 1*. Churchill Livingstone, London, United Kingdom; 1836: 1–8.
- Guyton AC, Coleman TG, Cowley AV Jr et al. Arterial pressure regulation. Overriding dominance of the kidneys in long-term regulation and in hypertension. *Am J Med* 1972; 52: 584–594.
- Aperia AC, Broberger CG, Soderlund S. Relationship between renal artery perfusion pressure and tubular sodium reabsorption. *Am J Physiol* 1971; 220: 1205–1212.
- Guyton AC. Blood pressure control—special role of the kidneys and body fluids. *Science* 1991; 252: 1813–1816.
- Dahl LK, Heine M, Thompson K. Genetic influence of the kidneys on blood pressure. Evidence from chronic renal homografts in rats with opposite predispositions to hypertension. *Circ Res* 1974; 40: 94–101.
- Dahl LK, Heine M. Primary role of renal homografts in setting chronic blood pressure levels in rats. *Circ Res* 1975; 36: 692–696.
- Bianchi G, Fox U, Di Francesco GF et al. Blood pressure changes produced by kidney cross-transplantation between spontaneously hypertensive rats and normotensive rats. *Clin Sci Mol Med* 1974; 47: 435–448.
- Kawabe K, Watanabe TX, Shiono K, Sokabe H. Influence on blood pressure of renal isografts between spontaneously hypertensive and normotensive rats, utilizing the F1 hybrids. *Jpn Heart J* 1978; 19: 886–894.
- Curtis JJ, Luke RG, Dustan HP et al. Remission of essential hypertension after renal transplantation. *N Engl J Med* 1983; 309: 1009–1015.
- Matchar DB, McCrory DC, Orlando LA et al. Systematic review: Comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. *Ann Intern Med* 2008; 148: 16–29.
- Le TH, Coffman TM. Targeting genes in the renin-angiotensin system. *Curr Opin Nephrol Hypertens* 2008; 17: 57–63.
- Hall JE. Control of sodium excretion by angiotensin II: Intrarenal mechanisms and blood pressure regulation. *Am J Physiol* 1986; 250: R960–R972.
- Navar LG, Kobori H, Prieto MC, Gonzalez-Villalobos RA. Intratubular renin-angiotensin system in hypertension. *Hypertension* 2011; 57: 355–362.
- Machnik A, Neuhofer W, Jantsch J et al. Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. *Nat Med* 2009; 15: 545–552.
- Machnik A, Dahlmann A, Kopp C et al. Mononuclear phagocyte system depletion blocks interstitial tonicity-responsive enhancer binding protein/vascular endothelial growth factor C expression and induces salt-sensitive hypertension in rats. *Hypertension* 2010; 55: 755–761.
- Herrera J, Ferrebuz A, MacGregor EG, Rodriguez-Iturbe B. Mycophenolate mofetil treatment improves hypertension in patients with psoriasis and rheumatoid arthritis. *J Am Soc Nephrol* 2006; 17: S218–S225.
- Kang YM, Ma Y, Zheng JP, et al. Brain nuclear factor- $\kappa$ B activation contributes to neurohumoral excitation in angiotensin II-induced hypertension. *Cardiovasc Res* 2009; 82: 503–512.
- Guggilam A, Haque M, Kerut EK, et al. TNF- $\alpha$  blockade decreases oxidative stress in the paraventricular nucleus and attenuates sympathoexcitation in heart failure rats. *Am J Physiol Heart Circ Physiol* 2007; 293: H599–H609.
- Purkayastha S, Zhang G, Cai D. Uncoupling the mechanisms of obesity and hypertension by targeting hypothalamic IKK- $\beta$  and NF- $\kappa$ B. *Nat Med* 2011; 17: 883–887.
- Mancia G, Grassi G. The autonomic nervous system and hypertension. *Circ Res* 2014; 114: 1804–1814.
- Grassi G, Cattaneo BM, Seravalle G et al. Baroreflex control of sympathetic nerve activity in essential and secondary hypertension. *Hypertension* 1998; 31: 68–72.
- Grassi G, Bertoli S, Seravalle G. Sympathetic nervous system: Role in hypertension and in chronic kidney disease. *Curr Opin Nephrol Hypertens* 2012; 21: 46–51.
- Spieker LE, Flammer AJ, Lüscher TF. The vascular endothelium in hypertension. *Handb Exp Pharmacol* 2006; 176: 249–283.
- Dharmashankar K, Widlansky ME. Vascular endothelial function and hypertension: Insights and directions. *Curr Hypertens Rep* 2010; 12: 448–455.
- Quinn U, Tomlinson LA, Cockcroft JR. Arterial stiffness. *JRSM Cardiovasc Dis* 2012; 1: 1–8.
- Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med* 2008; 359: 1811–1821.
- Bavishi C, Messerli FH, Rimoldi SF. Serum uric acid in primary hypertension: From innocent bystander to primum movens? *Hypertension* 2016; 67: 845–847.
- ERA-EDT Registry. *ERA-EDT Registry Annual Report 2015*. Academic Medical Center, Department of Medical Informatics, Amsterdam, the Netherlands, 2017. <https://www.era-edta-reg.org/files/annualreports/pdf/AnnRep2015.pdf>
- Neaton JD, Kuller LH, Wentworth D, Borhani NO. Total and cardiovascular mortality in relation to cigarette smoking, serum cholesterol concentration, and diastolic blood pressure among black and white males followed up for five years. *Am Heart J* 1984; 108: 759–769.

42. Shulman NB, Ford CE, Hall WD, Blaufox MD, Simon D, Langford HG, Schneider KA. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group. *Hypertension* 1989; 13: 180–193.
43. Griffin KA. Hypertensive kidney injury and the progression of chronic kidney disease. *Hypertension* 2017; 70: 687–694.
44. Laragh JH, Sealey J, Brunner HR. The control of aldosterone secretion in normal and hypertensive man: abnormal renin-aldosterone patterns in low renin hypertension. *Am J Med* 1972; 53(5): 649–63.

# BLOOD PRESSURE CONTROL IN EUROPE AND ELSEWHERE

# 4

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## INTRODUCTION

Over the last three decades, the status of high blood pressure (BP) has increased from being the fourth risk factor for global disease burden in 1990 to the first in 2010 (1). Consequently, the increase in annual mortality over the time period accounted for more than 2 million deaths (1). Improvement in BP control rates is probably one of the most beneficial steps that can improve life expectancy and the quality of life for millions of people with immediate and measurable results.

Despite advances in the knowledge of hypertension mechanisms, introduction of new antihypertensive drugs and a large number of campaigns alerting healthcare providers, stakeholders or populations, the number the hypertensives is still growing due to demographic factors. However, worldwide only a modest decrease in the proportion of the population with high BP was observed between 1980 and 2008 (2).

Based on the direct relationship between BP levels and cardiovascular and renal risk, two studies have analysed the trends in BP values across the last decades. The first analysed the changes in systolic blood pressure (SBP) between 1880 and 2006, including data on 5.2 million subjects (3). On average, global population SBP decreased slightly since 1980, 0.8 mmHg per decade in men and 1.0 in women, from initial age-standardised mean 128.1 mmHg in men and 124.4 in women. Trends, however, varied significantly across regions and countries. SBP is currently highest in low- and middle-income countries. The second study (4) expanded the number of subjects: 1479 population studies with a total of more than 19 million subjects were included; years of observation were from 1975 to 2015. The study concluded that during the past four decades, the number of people with elevated BP has risen worldwide, with the increase occurring mainly in low- and middle-income countries. Moreover, the highest levels of BP worldwide have shifted from high-income countries to low- and middle-income countries in South Asia and sub-Saharan Africa, while blood pressure has been persistently high in central and eastern Europe; although BP has decreased, it still in the high level.

These studies are not exempt from limitations, and despite the indisputable utility of awareness of BP trends, the studies do not show the results of the effort to control hypertension that are heterogeneous worldwide.

## CONTROL RATES AND TRENDS IN EUROPE

Knowledge of the status of control rates and trends over time in Europe is relevant due to the huge impact of cardiovascular diseases, the diseases most directly associated with hypertension. A clear picture of control rates and trends and establishing comparison among the countries is extremely difficult due to variability in the methodology applied, and even in the threshold to define hypertension control. Likewise, differences among regions in the same country exist. Recently we published a systematic review of the published articles from 1 January 2006 to 31 March 2015 (5), in which control rates were presented. Here we expand this review to 1 October 2017, using the descriptors of prevalence, incidence, control, hypertension and European countries. A total of 96 articles were found, in which only 29 contained relevant information concerning control rates and 13 contained surveys systematically performed over the years. A summary of the methodology and results of selected papers with control rates is shown in Table 4.1 (6–19,21–31,35) and those with several surveys in Table 4.2 (13,17,18,21,26–29,31–34,36).

The studies were performed in large cohorts of general population, in selected groups of age, older than 65 or than 80 years, or with specific diseases such as coronary heart disease (Table 4.1). Although the majority offered overall estimates of control rates, others provided data by age strata or ethnic subgroup. The majority of the studies considered control when BP was lower than 140/90 mmHg in the general population and lower than 130/80 in diabetic subjects. In some of the surveys in England, however, the threshold to define control is 150/90 mmHg (16). There are mainly studies from Western European countries, with a very few from Eastern Europe, in which the control rates are usually lower than those observed in Western Europe.

Overall, the rate of controlled subjects is less than 40% with the exception of Germany, which offers figures between 50 and 60% (10,26). England also provides in some of the surveys of general population rates of control near 50% in the general population, using the 140/90 mmHg as the threshold.

When the control rates were assessed in hypertensive subjects under antihypertensive treatment, the European Study on Cardiovascular Risk Prevention and

**Table 4.1** Summary of the methodology and BP control results from the literature in European patients with hypertension (published between 2008–2017)

| Reference                  | Country                            | Methodology                                                                                              | No. patients         | Patients with BP control <sup>a</sup> (%)                                                                                                                                                                                              |                                                                                                                                                                                                                                         |
|----------------------------|------------------------------------|----------------------------------------------------------------------------------------------------------|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                            |                                    |                                                                                                          |                      | All                                                                                                                                                                                                                                    | Treated                                                                                                                                                                                                                                 |
| Labeit et al. (6)          | Germany                            | Cross-sectional DETECT study in 2003                                                                     | 55,518               | –                                                                                                                                                                                                                                      | 21.4%                                                                                                                                                                                                                                   |
| Ninios et al. (7)          | Greece                             | Population-based study in patients ≥65 years old between 2002–2004                                       | 720                  | –                                                                                                                                                                                                                                      | 42.5%                                                                                                                                                                                                                                   |
| Sonkodi et al. (8)         | Hungary                            | BP screening in blue- and white-collar employees in 2005                                                 | 2012                 | –                                                                                                                                                                                                                                      | 18.5%                                                                                                                                                                                                                                   |
| Steiner (9)                | Hungary                            | BP screening project in white-collar employees in 2005                                                   | 1000                 | –                                                                                                                                                                                                                                      | 15.8%                                                                                                                                                                                                                                   |
| In der Schmitt (10)        | Germany                            | Cross-sectional data from general practice (CRISTOPH) in 2006                                            | 3355                 | 55.1%                                                                                                                                                                                                                                  | –                                                                                                                                                                                                                                       |
| Triantafyllou et al. (11)  | Greece                             | Cross-sectional survey in patients aged ≥65 years old in 2006                                            | 171                  | 32.8%                                                                                                                                                                                                                                  | 36.9%                                                                                                                                                                                                                                   |
| Wagner et al. (12)         | France                             | Cross-sectional, population-based survey between 2005 and 2007 (MONA LISA)                               | 4825                 | Men aged 35–64 years: 26.5%<br>35–74 years: 24.1%<br>Women aged 35–64 years: 45.8%<br>35–74 years: 38.9%                                                                                                                               | –                                                                                                                                                                                                                                       |
| Falaschetti et al. (13)    | England                            | Cross-sectional, nationally representative, random samples (HSE) of non-institutionalised adults in 2006 | 7478                 | 28%                                                                                                                                                                                                                                    | 52%                                                                                                                                                                                                                                     |
| Agyemang et al. (14)       | The Netherlands and United Kingdom | Secondary analyses of population-based studies between 2006                                              | 13,999               | White-Dutch: 9.1%<br>White-English: 11.1%<br>Dutch-African: 10.5%<br>English-African: 26.2%<br>English-Caribbean: 23.8%<br>Dutch South-Asian: 16.1%<br>English-Indian: 17.9%<br>English-Pakistani: 29.5%<br>English-Bangladeshi: 31.7% | White-Dutch: 40.9%<br>White-English: 45.3%<br>Dutch-African: 30.9%<br>English-African: 56.7%<br>English-Caribbean: 50.3%<br>Dutch South-Asian: 34.4%<br>English-Indian: 44.5%<br>English-Pakistani: 65.8%<br>English-Bangladeshi: 57.9% |
| Rodríguez-Roca et al. (15) | Spain                              | PRESCAP 2006 in patients ≥80 years old                                                                   | 923                  | –                                                                                                                                                                                                                                      | 35.6%                                                                                                                                                                                                                                   |
| Serumaga et al. (16)       | United Kingdom                     | Interrupted time series analysis in primary care using THIN database (2000 to 2007)                      | 470,725              | –                                                                                                                                                                                                                                      | 70% <sup>b</sup>                                                                                                                                                                                                                        |
| Cifková et al. (17)        | Czech Republic                     | Cross-sectional population survey 2007–2008                                                              | 13,972               | 24.6%                                                                                                                                                                                                                                  | 42.1%                                                                                                                                                                                                                                   |
| Banegas et al. (18)        | Spain                              | Field survey of total population 2008–2010                                                               | 4623<br>>60 year old | 25.4%                                                                                                                                                                                                                                  | –                                                                                                                                                                                                                                       |
| Paulsen et al. (19)        | Denmark                            | Danish General Practice Database from 2009–2011                                                          | 37,651               | 33.2%                                                                                                                                                                                                                                  | –                                                                                                                                                                                                                                       |

(Continued)



**Table 4.1 (Continued)** Summary of the methodology and BP control results from the literature in European patients with hypertension (published between 2008–2017)

| Reference                  | Country                             | Methodology                                                                                                    | No. patients                                           | Patients with BP control <sup>a</sup> (%) |                                                     |
|----------------------------|-------------------------------------|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|-------------------------------------------|-----------------------------------------------------|
|                            |                                     |                                                                                                                |                                                        | All                                       | Treated                                             |
| Agyemang et al. (14)       | The Netherlands                     | Cross-sectional study of Ghanaian adults in Amsterdam in 2010                                                  | 212                                                    | 15%                                       | 33%                                                 |
| Escobar et al. (21)        | Spain                               | Cross-sectional survey (PRESCAP) in primary care setting in 2010                                               | 12,961                                                 | –                                         | 2010: 46.3%                                         |
| Rodríguez-Roca et al. (22) | Spain                               | PRESCAP 2010 in patients ≥80 years old                                                                         | 13,420                                                 | –                                         | 40.8%                                               |
| Ferrari et al. (23)        | Western, Central and Eastern Europe | 5-year observational longitudinal cohort study (CLARIFY) in outpatients with stable CAD recruited in 2009/2010 | Western/Central Europe: 15,388<br>Eastern Europe: 3026 | –                                         | Western/Central Europe: ~55%<br>Eastern Europe: 47% |
| Catalá-López et al. (24)   | Spain                               | Systematic review and meta-analysis of epidemiological studies since 2000                                      | 341,632                                                | –                                         | 33%                                                 |
| Banegas et al. (25)        | Several countries                   | EURIKA                                                                                                         | 7641                                                   |                                           | 38%                                                 |
| Neuhauser et al. (26)      | Germany                             | Population surveys 2008–2011                                                                                   | 14,113                                                 | 58%                                       |                                                     |
| Barrios et al. (27)        | Spain                               | Primary Care                                                                                                   | 36,000                                                 |                                           | 47%                                                 |
| Tocci et al. (28)          | Italy                               | Population surveys 2005–2011                                                                                   | 211,591                                                | 39.7%                                     |                                                     |
| Falaszchetti et al. (29)   | England                             | Cross-sectional, nationally representative, random samples (HSE) of non-institutionalised adults in 2011       | 4466                                                   | 37%                                       | 63%                                                 |
| Tocci et al. (30)          | Italy                               | Observational study and clinical survey of 2011                                                                | 158,876                                                | –                                         | 37.0%                                               |
| Giampaoli et al. (31)      | Italy                               | Population surveys 2008–2012                                                                                   | 17,573                                                 | 32.8%                                     |                                                     |
| Kotseva et al. (32)        | Europe                              | EUROASPIRE IV (2012–2013)                                                                                      | 8456 with CHD                                          | 55.3%                                     |                                                     |
| Dregan A et al. (33)       | England                             | English Longitudinal Study of Ageing 2012–2013                                                                 | 24,699                                                 | 47–50%                                    |                                                     |
| Tocci et al. (34)          | Italy                               | Hypertension day 2013–2014:                                                                                    | 10,051                                                 |                                           | 57.6%                                               |
| Dorobantu et al. (35)      | Romania                             | SEPHAR III Population survey                                                                                   | 1790                                                   | 30.8%                                     |                                                     |

<sup>a</sup> Defined as ≥140/90 mmHg (<130/80 mmHg in patients with comorbid conditions) or being treated for high blood pressure, unless specified.

<sup>b</sup> BP <150/90 mmHg.

**Abbreviations:** CAD, coronary artery disease; CRISTOPH, Cardiovascular Risk Intervention Study to Optimise Treatment in Patients with Hypertension; CLARIFY, the prospective observational Longitudinal Registry of patients with stable coronary artery disease; HSE, Health Survey for England; PRESCAP, PRESión arterial en la población Española en los Centros de Atención Primaria; DETECT, Diabetes Cardiovascular Risk-Evaluation: Targets and Essential Data for Commitment of Treatment; THIN, The Health Improvement Netw.

**Table 4.2** Summary of the methodology and BP control results from the literature in European patients with hypertension (published between 2008–2015)

| Reference                 | Country        | Methodology                                                                                                                                                 | No. patients                                 | Patients with BP control <sup>a</sup> (%)                                                                   |                                                        |
|---------------------------|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
|                           |                |                                                                                                                                                             |                                              | All                                                                                                         | Treated                                                |
| Cifková R et al. (17)     | Czech Republic | Six independent cross-sectional population surveys from 1985 to 2007/2008                                                                                   | 13,972                                       | 1985: 3.9%<br>2007/2008: 24.6%                                                                              | 1985: 13.2%<br>2007/2008: 42.1%                        |
| Falaszchett E et al. (13) | England        | Two cross-sectional, nationally representative, random samples (HSE) of non-institutionalised adults in 2003 and 2006                                       | 2003: 8834<br>2006: 7478                     | 2003: 22%<br>2006: 28%                                                                                      | 2003: 46%<br>2006: 52%                                 |
| Falaszchett E et al. (29) | England        | Five cross-sectional, nationally representative, random samples (HSE) of non-institutionalised adults between 1994 and 2011                                 | 1994: 12,117<br>2011: 4466                   | 1994: 11%<br>2011: 37%                                                                                      | 1994: 33%<br>2011: 63%                                 |
| Tocci et al. (34)         | Italy          | Hypertension day                                                                                                                                            | 10,051                                       |                                                                                                             | 2004–2010: 50%<br>2011–2012: 55.5%<br>2013–2014: 57.6% |
| Kotseva et al. (32)       | Europe         | EUROASPIRE                                                                                                                                                  | 8456 with CHD                                | EA II (99-00): 45.7%<br>EA III (06-07): 47.8%<br>EA IV (12-13): 55.3%                                       |                                                        |
| Dregan A. et al. (33)     | England        | English Longitudinal Study of Ageing                                                                                                                        | 24,699                                       | More or less than 80 yr<br>2002–2003: 37–32%<br>2004–2005: 31–40%<br>2008–2009: 37–44%<br>2012–2013: 47–50% |                                                        |
| Ruckert et al. (36)       | Germany        | CARLA (baseline 2002–2006 and follow-up 2007–2010), KORA (baseline 1999–2001 and follow-up 2006–2008) and SHIP (baseline 1997–2001 and follow-up 2002–2006) | 4683 diabetics and nondiabetics              | Nondiabetics 10 to 26%<br>Diabetics 20 to 40%                                                               |                                                        |
| Banegas et al. (18)       | Spain          | Field survey of total population                                                                                                                            | 4623<br>>60 year old                         | 2000–2001: 16.3%<br>2008–2010: 25.4%                                                                        |                                                        |
| Giampaoli et al. (31)     | Italy          | Population surveys                                                                                                                                          | 17,573                                       | 1998–2002: 12.1%<br>2008–2012: 32.8%                                                                        |                                                        |
| Neuhauser et al. (26)     | Germany        | Population surveys                                                                                                                                          | 14,113                                       | 1988: 44%<br>2008–2011: 58%                                                                                 |                                                        |
| Escobar C et al. (21)     | Spain          | Three cross-section surveys (PRESCAP) in primary care setting in 2002, 2006 and 2010                                                                        | 2002: 12,754<br>2006: 10,520<br>2010: 12,961 | –                                                                                                           | 2002: 31.1<br>2006: 41.4<br>2010: 46.3                 |
| Barrios et al. (27)       | Spain          | Primary Care                                                                                                                                                | 36,000<br>HTN treated                        | 2002: 36%<br>2006: 41%<br>2010: 47%                                                                         |                                                        |
| Tocci et al. (28)         | Italy          | Population surveys                                                                                                                                          | 211,591                                      | 2000–2006: 18.4%<br>2005–2011: 39.7%                                                                        |                                                        |

Management in Usual Daily Practice (EURIKA) (25), a cross-sectional study of the status of primary cardiovascular disease (CVD) prevention, identified that 38.8% of patients achieved a target BP. The rates of control, however, have improved to around 50% or even higher. Likewise, the rate of control reported by the EUROASPIRE IV was 55.6% in subjects with a previous coronary event (32). The observed improvement is the result of different interventions in many of the European countries.

It is worth noting the different rate of control in minorities living in European countries, mainly in the UK and the Netherlands. The control rates in the general population of minorities are low, around 20%, while the control in the treated subjects is twice that (20).

Considering control rates trends over time, 13 publications reported surveys on hypertension control rates over time with the same or similar methodology (Table 4.2). As in the prevalence studies, Western European countries predominated. In both general population studies or in hypertensive treated subjects, the rate of control improved between 10–20% in a 10-year time period.

## INDIRECT ASSESSMENT OF CONTROL

Recognizing the difficulties in obtaining timely and comparable population surveys, alternative methods to assess the BP status across populations could be an important quality indicator for health systems. Assessing the incidence and trends of hypertension-induced clinical conditions could prove useful in this regard. Among the options for a surveillance measure, stroke incidence and/or mortality presents an attractive option (37).

In a study by our group, a positive relationship exists between stroke mortality and the average of SBP at the country level in the 25 in which BP values were available (38). The relationship was quantitatively larger in women than it was in men. Likewise, the relationship varied with age, being more apparent in the younger age strata. We acknowledge the uncertainties of the SBP values available and that the data are often not comparable across surveys, however the positive trends between stroke mortality and SBP reported from population surveys supports the hypothesis that stroke mortality is a rough proxy of the hypertension status in a community.

If we assume that stroke mortality can serve as a proxy for average BP in a population, the data presented here clearly demonstrate the necessity to adopt actions to increase the diagnosis, treatment and hypertension control in the countries where the burden of hypertension sequelae is still growing. Policies to increase the rate of BP control offer the best approach, while primary prevention strategies must also be implemented.

## FACTORS RELATED TO SHORTNESS OF CONTROL RATES

Overall, an improvement in BP control is observed in treated patients; however, there is still an urgent need to improve BP control rates in untreated and treated populations. The continuing need to improve the control of high BP has been highlighted in a report from the World

Health Organization (39) and a fact sheet issued by the World Hypertension League and the International Society of Hypertension (40).

In 2008, a white paper was published by a group of researchers in hypertension with a call for action to improve the rates of control. The manuscript identified the key challenges in the treatment of hypertension and suggested recommendations for improving control (41). Despite some improvements in 2016, a new publication (5) points to the fact that six challenges are still present: inadequate primary prevention, faulty awareness of risk, lack of simplicity in the treatments, therapeutic inertia, insufficient patient empowerment and unsupportive healthcare systems. In the last few years a new challenge has emerged – the discrepancies and changes in the BP goals provided by guidelines, which contribute to physician uncertainties.

For continuing advances in control, supplementary effort is necessary, as what has been achieved in the past reflects a slow improvement, with the exception of successful program such is the Canadian Hypertension Educational Program (CHEP), a professional education program which provides annually updated simple recommendations and clinical practice guidelines for the detection, treatment and control of hypertension with control rates around 68% in the general population and greater than 75% among the treated subjects (20). Recently, some programs have been launched in some European countries (France and Italy) with the objective of achieving 70% control rates.

In order to progress in hypertension control, a few actions can produce success. Among them, simplify the BP treatment target to <140/90 mmHg for the majority of patients and the treatment options with a single pill combination of drugs. In parallel, encourage patient empowerment and involve healthcare systems, shifting the focus away from cost. These simple key actions should form the basis of hypertension management in Europe going forward, ensuring that more patients are achieving BP control in the future, and thereby reducing cardiovascular morbidity and mortality.

## REFERENCES

1. Lim SS, Vos T, Flaxman AD et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012 December 15; 380(9859): 2224–2260.
2. WHO. Global status report on noncommunicable diseases. 2010 [cited July 2015]; Available from: [http://www.who.int/nmh/publications/ncd\\_report2010/en/](http://www.who.int/nmh/publications/ncd_report2010/en/).
3. Danaei G, Finucane MM, Lin JK et al. National, regional, and global trends in systolic blood pressure since 1980: Systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. *Lancet* 2011; 377: 568–577.
4. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: A pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* 2017; 389: 37–55.
5. Redon J, Mourad JJ, Schmieder RE et al. Why in 2016 are patients with hypertension not 100% controlled? A call to action. *J Hypertens* 2016; 34: 1480–1488.
6. Labeit AM, Klotsche J, Pieper L et al. Changes in the prevalence, treatment and control of hypertension in Germany? A clinical-epidemiological study of 50,000 primary care patients. *PLOS ONE* 2012; 7:e52229.
7. Ninios I, Ninios V, Lazaridou F et al. Gender-specific differences in hypertension prevalence, treatment, control, and associated conditions among the elderly: Data from a Greek population. *Clin Exp Hypertens* 2008; 30: 327–e52337.

8. Sonkodi B, Sonkodi S, Steiner S et al. High prevalence of prehypertension and hypertension in a working population in Hungary. *Am J Hypertens* 2012; 25: 204–208.
9. Steiner S, Helis E, Chen L et al. A cross-national comparative study of blood pressure levels and hypertension prevalence in Canada and Hungary. *J Hypertens* 2012; 30: 2105–2111.
10. In der Schmitten J, Wegscheider K, Abholz HH, Mortsiefer A. Risk-adjusted versus overall blood pressure control rate for identifying the need for intensified cardiovascular risk reduction: Lessons from a cross-sectional study. *Eur J Prev Cardiol* 2013; 20: 972–979.
11. Triantafyllou A, Douma S, Petidis K et al. Prevalence, awareness, treatment and control of hypertension in an elderly population in Greece. *Rural Remote Health* 2010; 10: 1225.
12. Wagner A, Sadoun A, Dallongeville J et al. High blood pressure prevalence and control in a middle-aged French population and their associated factors: The MONA LISA study. *J Hypertens* 2011; 29: 43–50.
13. Falaschetti E, Chaudhury M, Mindell J, Poulter N. Continued improvement in hypertension management in England: Results from the Health Survey for England 2006. *Hypertension* 2009; 53: 480–486.
14. Agyemang C, Kunst A, Bhopal R et al. A cross-national comparative study of blood pressure and hypertension between English and Dutch South-Asian- and African-origin populations: The role of national context. *Am J Hypertens* 2010; 23: 639–648.
15. Rodriguez-Roca GC, Pallares-Carratala V, Alonso-Moreno FJ et al. Blood pressure control and physicians' therapeutic behavior in a very elderly Spanish hypertensive population. *Hypertens Res* 2009; 32: 753–758.
16. Serumaga B, Ross-Degnan D, Avery AJ et al. Effect of pay for performance on the management and outcomes of hypertension in the United Kingdom: Interrupted time series study. *BMJ* 2011; 342:d108.
17. Cifkova R, Skodova Z, Bruthans J et al. Longitudinal trends in cardiovascular mortality and blood pressure levels, prevalence, awareness, treatment, and control of hypertension in the Czech population from 1985 to 2007/2008. *J Hypertens* 2010; 28: 2196–2203.
18. Banegas JR, Navarro-Vidal B, Ruilope LM et al. Trends in hypertension control among the older population of Spain from 2000 to 2001 to 2008 to 2010: Role of frequency and intensity of drug treatment. *Circ Cardiovasc Qual Outcomes* 2015; 8: 67–76.
19. Paulsen MS, Andersen M, Thomsen JL et al. Multimorbidity and blood pressure control in 37 651 hypertensive patients from Danish general practice. *J Am Heart Assoc* 2013; 2:e004531.
20. Leung AA, Daskalopoulou SS, Dasgupta K et al. Hypertension Canada. Hypertension Canada's 2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults. *Can J Cardiol* 2017; 33: 557–576.
21. Escobar C, Barrios V, Alonso-Moreno FJ et al. Evolution of therapy inertia in primary care setting in Spain during 2002–2010. *J Hypertens* 2014; 32: 1138–1145.
22. Rodriguez-Roca GC, Llisterri JL, Prieto-Diaz MA et al. Blood pressure control and management of very elderly patients with hypertension in primary care settings in Spain. *Hypertens Res* 2014; 37: 166–171.
23. Ferrari R, Ford I, Greenlaw N et al. Geographical variations in the prevalence and management of cardiovascular risk factors in outpatients with CAD: Data from the contemporary CLARIFY registry. *Eur J Prev Cardiol* 2015; 22: 1056–1065.
24. Catala-Lopez F, Sanfelix-Gimeno G, Garcia-Torres C et al. Control of arterial hypertension in Spain: A systematic review and meta-analysis of 76 epidemiological studies on 341 632 participants. *J Hypertens* 2012; 30: 168–176.
25. Banegas JR, Lopez-Garcia E, Dallongeville J et al. Achievement of treatment goals for primary prevention of cardiovascular disease in clinical practice across Europe: The EURIKA study. *Eur Heart J* 2011; 32: 2143–2152.
26. Neuhauser HK, Adler C, Rosario AS et al. Hypertension prevalence, awareness, treatment and control in Germany 1998 and 2008–11. *J Hum Hypertens* 2015; 29: 247–253.
27. Barrios V, Escobar C, Alonso-Moreno FJ et al. Evolution of clinical profile, treatment and blood pressure control in treated hypertensive patients according to the sex from 2002 to 2010 in Spain. *J Hypertens* 2015; 33: 1098–1107.
28. Tocci G, Ferrucci A, Pontremoli R et al. Blood pressure levels and control in Italy: Comprehensive analysis of clinical data from 2000–2005 and 2005–2011 hypertension surveys. *J Hum Hypertens* 2015; 29: 696–701.
29. Falaschetti E, Mindell J, Knott C, Poulter N. Hypertension management in England: A serial cross-sectional study from 1994 to 2011. *Lancet* 2014; 383: 1912–1919.
30. Tocci G, Rosei EA, Ambrosioni E et al. Blood pressure control in Italy: Analysis of clinical data from 2005–2011 surveys on hypertension. *J Hypertens* 2012; 30: 1065–1074.
31. Giampaoli S, Palmieri L, Donfrancesco C et al. Cardiovascular health in Italy. Ten-year surveillance of cardiovascular diseases and risk factors: Osservatorio Epidemiologico Cardiovascolare/Health Examination Survey 1998–2012. *Eur J Prev Cardiol* 2015; 22(Suppl 2): 9–37.
32. Kotseva K, De Bacquer D, Jennings C et al. Time trends in lifestyle, risk factor control, and use of evidence-based medications in patients with coronary heart disease in Europe: Results from 3 EUROASPIRE surveys, 1999–2013. *Glob Heart* 2017; 12(4): 315–322.e3.
33. Dregan A, Ravindrarajah R, Hazra N et al. Longitudinal trends in hypertension management and mortality among octogenarians: Prospective Cohort Study. *Hypertension* 2016; 68: 97–105.
34. Tocci G, Muiesan ML, Parati G et al. Trends in prevalence, awareness, treatment, and control of Blood Pressure recorded from 2004 to 2014 during World Hypertension Day in Italy. *J Clin Hypertens (Greenwich)* 2016; 18: 551–556.
35. Dorobantu M, Tautu OF, Dimulescu D et al. Perspectives on hypertension's prevalence, treatment and control in a high cardiovascular risk East European country: Data from the SEPHAR III survey. *J Hypertens* 2018 Mar; 36(3): 690–700.
36. Rückert IM, Baumert J, Schunk M et al. Blood pressure control has improved in people with and without type 2 diabetes but remains suboptimal: A longitudinal study based on the German DIAB-CORE consortium. *PLOS ONE* 2015; 10:e0133493.
37. Cooper RS. Using public health indicators to measure the success of hypertension control. *Hypertension* 2007; 49: 773–774.
38. Redón J, Cea-Calvo L, Lozano JV et al. Differences in blood pressure control and stroke mortality across Spain: The Prevención de Riesgo de Ictus (PREV-ICTUS) study. *Hypertension* 2007; 49: 799–805.
39. WHO. A global brief on hypertension. Silent killer, global public health crisis. 2013 [cited July 2015]; Available from: [http://apps.who.int/iris/bitstream/10665/79059/1/WHO\\_DCO\\_WHD\\_2013.2\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/79059/1/WHO_DCO_WHD_2013.2_eng.pdf?ua=1).
40. WHO I. High blood pressure: Why prevention and control are urgent and important. A 2014 fact sheet from the World Hypertension League and the International Society of Hypertension. 2014 [cited July 2015]; Available from: <http://ish-world.com/news/a/WHL-and-ISH-Hypertension-Fact-Sheet/>.
41. Redon J, Brunner HR, Ferri C et al. Practical solutions to the challenges of uncontrolled hypertension: A white paper. *J Hypertens Suppl* 2008; 26:S1–14.

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## INTRODUCTION

The detrimental effect of socioeconomic status upon all-cause mortality has been well described in the literature and is confirmed in the most recent data, as for instance the 25 × 25 multicohort initiative (1). Nevertheless, the valid assessment and conceptualization of socioeconomic status is challenging, since it represents a composite notion that integrates financial, professional and education status; all three are interrelated but not obligatorily overlapping components (2).

The relevance of socioeconomic deprivation as a factor contributing to the occurrence of coronary heart disease has been recognized since the 1960s, reversing the earlier beliefs that coronary heart disease is a ‘manager’s disease’ (3,4). In 1976, the Oslo study encompassed 14,677 men aged 40–49 without known cardiovascular disease and took a step beyond the overall examination of coronary heart disease, showing that education and income are related to the presence of a variety of coronary risk factors; systolic blood pressure, serum cholesterol and triglyceride levels as well as the prevalence of cigarette smoking increased along with lower socioeconomic status in the cohort of Norwegian men (5). Studies published in subsequent decades, from various countries, further validated the initial results (6–10).

More recent studies have followed the aforementioned paradigm and examined the associations between socioeconomic determinants and hypertension as a corollary risk factor for coronary artery disease. Taking into account the methodological challenges in the approach of socioeconomic determinants, the published studies in the literature have attempted various conceptualization strategies, either examining the socioeconomic components separately or addressing composite indices, as well as proceeding to comparisons between countries. Along with the accumulation of data, systematic reviews and meta-analyses examining the relevance of socioeconomic status in hypertension have appeared in recent years. In this chapter, we focus on and review studies as well as meta-analyses that examine the associations between socioeconomic indices and hypertension. We will also discuss potential mechanisms underlying the associations and critically address limitations of the published literature.

## COMPARISONS BETWEEN COUNTRIES

Comparisons across countries may offer valuable information about the association between hypertension and socioeconomic determinants, as countries vary considerably in terms of income and attained education. Nevertheless, despite the striking messages of descriptive, cross-national comparisons, such ecological approaches greatly suffer from the effects of uncontrolled confounders. For instance, differences in the genetic component (ethnicity), should be taken into consideration, as hypertension is more frequent in blacks (11,12); in addition, gradients in smoking, physical activity (13) and nutrition patterns (14) affecting hypertension rates could account at least partly for the findings and do not allow a straightforward inference about the effects of socioeconomic gradients.

At the cross-country comparison level, a meta-analysis published in 2015 synthesized a total of 242 studies from 45 countries, which included data on 1,494,609 adults. Overall, the prevalence of hypertension was 32.3% (95% CI: 29.4–35.3%); the highest estimates were reported by the Latin America and Caribbean region (39.1%, 95% CI: 33.1–45.2%). The association with income was intriguing because the prevalence of hypertension was highest in upper middle-income countries (37.8%, 95% CI: 35.0–40.6%) but lowest in the low-income countries (23.1%, 95% CI: 20.1–26.2%). In simple terms, the data of this meta-analysis imply that about 1 in 3 adults in the developing world is hypertensive and portrays the significant burden of hypertension in middle- and low-income countries, that should not be neglected (15). Similarly, the 2017 report of the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) investigators evaluated 10 community-dwelling cohorts from three continents and highlighted that the higher social and economic development, measured by the Human Development Index, was associated with lower rates of conventional as well as ambulatory hypertension (16).

Importantly, the 2013 Global Brief on Hypertension by the World Health Organization highlighted that the age-standardized prevalence of raised blood pressure in adults is highest in Africa compared to the other continents (17); accordingly, the brief also emphasized that sub-Saharan



African countries present with the highest cerebrovascular disease mortality rates. These alarming figures have prompted the Pan-African Society of Cardiology (PASCAR) to issue a roadmap to achieve 25% hypertension control in Africa by 2025, underlining that the majority of the sub-Saharan countries do not have a clear hypertension policy (18).

Given that two-thirds of the 1 billion people with hypertension globally live in low- and middle-income countries, another meta-analysis focused especially on the latter and aimed to examine whether socioeconomic determinants were associated with hypertension, especially in rural areas. Although educational status correlated inversely with hypertension in East Asia, variable associations were reported by the meta-analysis across the examined regions, whereas regions such as Latin America were underrepresented in terms of studies addressing this research question (19).

On the other hand, studies associating higher socioeconomic status with hypertension in low-income countries have appeared, underlining local particularities in the African context. For instance, a relatively large cross-sectional survey of 9254 participants in the urban capital region of Tanzania demonstrated a positive association between hypertension and socioeconomic status, reflecting that the ongoing urbanization and affluence of African regions may account for the further increase in hypertension rates (20). It seems therefore that country-specific factors and variable degrees of urbanization may modify the associations between socioeconomic determinants and hypertension, with variable patterns in rural and urban areas.

### **SOCIOECONOMIC STATUS AND HYPERTENSION: META-ANALYSES AND CURRENT CONCEPTS**

Summarizing the accumulating evidence, a seminal meta-analysis published in 2015 synthesized 51 studies and demonstrated the increased risk of hypertension in the lowest socioeconomic strata in terms of all three relevant indicators, namely income (pooled OR = 1.19, 95% CI: 0.96–1.48), occupation (pooled OR = 1.31, 95% CI: 1.04–1.64) and education (pooled OR = 2.02, 95% CI: 1.55–2.63). Significant associations emerged in high-income countries and were especially evident in women (21); the meta-analysis, however, confirmed the distinct correlation between higher socioeconomic status and hypertension in Africa that was detailed in the previous section of this chapter. Studies published after the seminal meta-analysis have consistently supported the link between hypertension and lower socioeconomic status, from diverse non-African populations (22–24). Recent evidence has confirmed that the association between lower socioeconomic status and hypertension is present as early as in childhood and adolescence, according to studies from various countries, including China (25), Canada (26) and Europe (27).

The Multi-Ethnic Study of Atherosclerosis (MESA), a prospective cohort study of subclinical CVD in 6814 adults aged 45–84 years from six sites and states in the US adopted a multidimensional assessment of neighbourhood socioeconomic status through a scale that integrated level of wealth,

income, education, and occupation. This study, published in 2017, highlighted that adverse social environment was a crucial factor associated with higher prevalence of hypertension, diabetes, depressive symptoms, elevated inflammatory biomarkers and less access to health insurance (28). From a methodological viewpoint, the reproducibility of associations at the level of composite indices that may describe socioeconomic status globally further supports the role of socioeconomic status as a factor affecting the occurrence of hypertension. The association between neighbourhood disadvantage and hypertension has also been supported by other studies, such as the University of Alabama at Birmingham Study of Ageing, which showed that neighbourhood deprivation was associated with higher prevalence of hypertension and poor BP control (29).

Apart from the efforts to objectively express and quantify socioeconomic status and its components, a level of subjective self-perception of socioeconomic status in relation to society as a whole may also be relevant in this debate. A recent meta-analysis published in 2016 evaluated the association between subjective social status, namely the individual's perception of his/her position in the social hierarchy, and the presence of risk factors for coronary artery disease, synthesizing nine studies. Comparing the bottom versus the top of the subjective social status ladder measures such as income, education or occupation, the OR (odds ratio) for hypertension was 1.88 (95% CI: 1.27–2.79); this pattern was reproducible also in coronary artery disease as well as other risk factors, such as diabetes and dyslipidemia. Hence it seems that apart from the actual socioeconomic status, the self-perception of one's own status on the social hierarchy might exert health effects beyond those exerted by the actual socioeconomic determinants (30).

Taking an additional step, a meta-analysis evaluated an interesting aspect; that is, whether socioeconomic status may also act through fostering nonadherence to antihypertensive drugs. The meta-analysis synthesized 30 studies that reported on 40 cohorts, and uncovered a pooled adjusted risk estimate for nonadherence according to socioeconomic status (high vs. low) equal to 0.89 (95% CI: 0.87–0.92); nevertheless, the authors emphasized that these cohorts as a rule did not adopt comprehensive, multidimensional measures (31). Accordingly, subsequent studies also highlighted the association between higher education and hypertension control (32).

### **POSSIBLE MECHANISMS**

Multiple mechanisms may link socioeconomic status and hypertension. Lower socioeconomic status may signal suboptimal awareness of hypertension prevention and BP control, restricted accessibility to preventive health services and lack of adherence to medical treatment (33). Lower socioeconomic status may also be accompanied by health-related lifestyles and behaviours that contribute to the existence of hypertension. Subjects of lower education or income may also consume larger amounts of alcohol (34) and smoke to a greater extent (35,36), and unhealthy choices of nutrition and obesity prevail in this group (37). Interestingly, a meta-analysis published in 2017 showed that people of low socioeconomic status also consume greater amounts of sodium, a fact that may also contribute to the socioeconomic disparities in hypertension



patterns (38). It is hard to unequivocally disentangle the confounding or mediating nature of such associations; however, this network of interrelations is of paramount importance, and elaborate methodological tools, such as path analysis (39) and structural equation modelling (40), attempt to quantify the relative contributions of the aforementioned component causes in shaping the occurrence of coronary heart disease.

Apart from the biological factors, the psychological component cannot be overlooked. Unemployment or fear of unemployment may impose a considerable level of psychosocial stress that is in turn detrimental for hypertension; to this direction, a meta-analysis on hypertension and psychosocial stress supported a positive association, noting that stress in psychosocial terms can be induced by socioeconomic changes and stress at the workplace (41). In addition, worse living and working conditions may delay the early diagnosis and treatment of hypertension, further imposing the burden of complications.

In parallel, at a global and environmental level, the fast, unplanned urbanization of lower-income countries may foster an unhealthy environment in which sedentary behaviour and fast food consumption prevail, propagating the modern epidemic of hypertension (17). Notably, the notion of an unhealthy environment does not exclusively pertain to the lower-income countries but is also relevant in the cities of the Western world. As an example, an impressive Canadian study portrayed the environmentally deleterious role of non-walkable neighbourhoods in the incidence of hypertension; examining 1057 propensity score-matched pairs, the study observed that subjects who changed neighbourhoods from a low- to a high-walkability one benefited from a significantly lower risk of incident hypertension (42). The neighbourhood environment may well interact with other style factors; another report of the MESA study showed that healthy food availability in the neighbourhood was associated with a 12% lower rate of hypertension (43).

Nevertheless, reverse causality might interfere with the findings of relevant studies. On the one hand, socioeconomic status could positively affect health, but on the other hand good health could positively affect socioeconomic status. The main causal path seems to be from socioeconomic status to hypertension and not vice versa, given that hypertension – at least in the early stages – is not associated with disability; nevertheless, such aspects should be kept in mind during the interpretation of study findings, since the observed social inequalities inherently integrate social causation as well as health selection (44).

## CONCLUSION

Socioeconomic determinants seem to be risk factors for hypertension. To date, prevention of hypertension has focused on the control of modifiable lifestyle and behavioural risk factors, such as restriction of salt intake, maintenance of normal weight, promotion of physical activity and avoidance of smoking. However, the vulnerability of disadvantaged socioeconomic groups in terms of the disproportionate noncommunicable disease burden suggests that interventions should be designed to attenuate the effects of inequalities, or at least special intervention campaigns should be developed to effectively target the groups that live in socioeconomic adverse environments.

## REFERENCES

- Stringhini S, Carmeli C, Jokela M et al. Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: A multicohort study and meta-analysis of 1.7 million men and women. *Lancet* 2017 March 2; 389(10075): 1229–1237.
- Centers for Disease Control and Prevention. Social Determinants of Health. December 01, 2017; Available from: <http://www.cdc.gov/socialdeterminants/Definitions.html>.
- Pell S, D'Alonzo CA. Blood pressure, body weight, serum cholesterol, and smoking habits among executives and non-executives. *J Occup Med* 1961 October; 67–70.
- Shekelle RB, Ostfeld AM, Paul O. Social status and incidence of coronary heart disease. *J Chronic Dis* 1969 December; 22(6): 381–394.
- Holme I, Helgeland A, Hjermann I et al. Coronary risk factors and socioeconomic status. The Oslo study. *Lancet* 1976 December 2; 2(8000): 1396–1398.
- Knipping GM, Kostner GM, Holasek A. Studies on the composition of pig serum lipoproteins. *Isolation and characterization of different apoproteins. Biochim Biophys Acta* 1975 May 3; 393(1): 88–99.
- Marmot MG, Shipley MJ, Rose G. Inequalities in death-specific explanations of a general pattern? *Lancet* 1984 May; 1(8384): 1003–1006.
- Rose G, Marmot MG. Social class and coronary heart disease. *Br Heart J* 1981 January; 45(1): 13–19.
- Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: A review of the literature. *Circulation* 1993 October; 88(4 Pt 1): 1973–1998.
- Singh-Manoux A, Nabi H, Shipley M et al. The role of conventional risk factors in explaining social inequalities in coronary heart disease: The relative and absolute approaches to risk. *Epidemiology* 2008 July; 19(4): 599–605.
- Opie LH, Seedat YK. Hypertension in sub-Saharan African populations. *Circulation* 2005 December; 112(23): 3562–3568.
- Lackland DT. Racial differences in hypertension: Implications for high blood pressure management. *Am J Med Sci* 2014 August; 348(2): 135–138.
- Liu X, Zhang D, Liu Y et al. Dose-response association between physical activity and incident hypertension: A systematic review and meta-analysis of cohort studies. *Hypertension* 2017 May; 69(5): 813–820.
- Li B, Li F, Wang L, Zhang D. Fruit and vegetables consumption and risk of hypertension: A meta-analysis. *J Clin Hypertens (Greenwich)* 2016 May; 18(5): 468–476.
- Sarki AM, Nduka CU, Stranges S et al. Prevalence of hypertension in low- and middle-income countries: A systematic review and meta-analysis. *Medicine (Baltimore)* 2015 December; 94(50): e1959.
- Melgarejo JD, Maestre GE, Thijs L et al. Prevalence, treatment, and control rates of conventional and ambulatory hypertension across 10 populations in 3 continents. *Hypertension* 2017 July; 70(1): 50–58.
- World Health Organization. *A Global Brief on Hypertension*. WHO, Geneva, Switzerland; 2013.
- Dzudie A, Rayner B, Ojji D et al. Roadmap to achieve 25% hypertension control in Africa by 2025. *Cardiovasc J Afr* 2017 July/August; 28(4): 262–272.
- Busingye D, Arabshahi S, Subasinghe AK et al. Do the socioeconomic and hypertension gradients in rural populations of low- and middle-income countries differ by geographical region? A systematic review and meta-analysis. *Int J Epidemiol* 2014 October; 43(5): 1563–277.
- Bovet P, Ross AG, Gervasoni JP et al. Distribution of blood pressure, body mass index and smoking habits in the urban population of Dar es Salaam, Tanzania, and associations with socioeconomic status. *Int J Epidemiol* 2002 February; 31(1): 240–247.
- Leng B, Jin Y, Li G et al. Socioeconomic status and hypertension: A meta-analysis. *J Hypertens* 2015 February; 33(2): 221–229.
- Park CS, Ha KH, Kim HC et al. The association between parameters of socioeconomic status and hypertension in Korea: The Korean Genome and Epidemiology Study. *J Korean Med Sci* 2016 December; 31(12): 1922–1928.
- Choi HM, Kim HC, Kang DR. Sex differences in hypertension prevalence and control: Analysis of the 2010–2014 Korea National Health and Nutrition Examination Survey. *PLOS ONE* 2017; 12(5): e0178334.
- Marden JR, Walter S, Kaufman JS, Glymour MM. African Ancestry, Social Factors, and Hypertension Among Non-Hispanic

- Blacks in the Health and Retirement Study. *AAAS Annual Meeting and Science Innovation Exposition*. 2016; 62(1): 19–35.
25. Ip P, Ho FK, So HK et al. Socioeconomic gradient in childhood obesity and hypertension: A multilevel population-based study in a Chinese Community. *PLOS ONE* 2016; 11(6):e0156945.
  26. Shi Y, de Groh M, Bancej C. Socioeconomic gradients in cardiovascular risk in Canadian children and adolescents. *Health Promot Chronic Dis Prev Can* 2016 February; 36(2): 21–31.
  27. Kaczmarek M, Stawinska-Witoszynska B, Krzyzaniak A et al. Who is at higher risk of hypertension? Socioeconomic status differences in blood pressure among Polish adolescents: A population-based ADOPLNOR study. *Eur J Pediatr* 2015 November; 174(11): 1461–1473.
  28. Hussein M, Diez Roux AV, Mujahid MS et al. Unequal exposure or unequal vulnerability? Contributions of neighborhood conditions and cardiovascular risk factors to socioeconomic inequality in incident cardiovascular disease in the multi-ethnic study of atherosclerosis. *Am J Epidemiol* 2018 Jul 1; 187(7): 1424–1437.
  29. Buys DR, Howard VJ, McClure LA et al. Association between neighborhood disadvantage and hypertension prevalence, awareness, treatment, and control in older adults: Results from the University of Alabama at Birmingham Study of Aging. *Am J Public Health* 2015 June; 105(6): 1181–1188.
  30. Tang KL, Rashid R, Godley J, Ghali WA. Association between subjective social status and cardiovascular disease and cardiovascular risk factors: A systematic review and meta-analysis. *BMJ Open* 2016 March 1; 6(3): e010137.
  31. Alsabbagh MH, Lemstra M, Eurich D et al. Socioeconomic status and nonadherence to antihypertensive drugs: A systematic review and meta-analysis. *Value Health* 2014 March; 17(2): 288–296.
  32. Chor D, Pinho Ribeiro AL, Sa Carvalho M et al. Prevalence, awareness, treatment and influence of socioeconomic variables on control of high blood pressure: Results of the ELSA-Brasil Study. *PLOS ONE* 2014; 10(6):e0127382.
  33. Grotto I, Huerta M, Sharabi Y. Hypertension and socioeconomic status. *Curr Opin Cardiol* 2008 July; 23(4): 335–339.
  34. Jones L, Bates G, McCoy E, Bellis MA. Relationship between alcohol-attributable disease and socioeconomic status, and the role of alcohol consumption in this relationship: A systematic review and meta-analysis. *BMC Public Health* 2015 April 1; 1: 00–1.
  35. Casetta B, Videla AJ, Bardach A et al. Association between cigarette smoking prevalence and income level: A systematic review and meta-analysis. *Nicotine Tob Res* 2017 November; 19(12): 1401–1407.
  36. Centers for Disease Control and Prevention. Cigarette Smoking and Tobacco Use Among People of Low Socioeconomic Status. 2017. Available from: <https://www.cdc.gov/tobacco/disparities/low-ses/index.htm>.
  37. Newton S, Braithwaite D, Akinyemiju TF. Socio-economic status over the life course and obesity: Systematic review and meta-analysis. *PLOS ONE* 2017; 12(5): e0177151.
  38. de Mestral C, Mayen AL, Petrovic D et al. Socioeconomic determinants of sodium intake in adult populations of high-income countries: A systematic review and meta-analysis. *Am J Public Health* 2017 April; 107(4): 563.
  39. Kershaw KN, Droomers M, Robinson WR et al. Quantifying the contributions of behavioral and biological risk factors to socioeconomic disparities in coronary heart disease incidence: The MORGEN study. *Eur J Epidemiol* 2013 October; 28(10): 807–814.
  40. Cois A, Ehrlich R. Analysing the socioeconomic determinants of hypertension in South Africa: A structural equation modelling approach. *BMC Public Health* 2014 May; 1: 14.
  41. Liu MY, Li N, Li WA, Khan H. Association between psychosocial stress and hypertension: A systematic review and meta-analysis. *Neurol Res* 2017 June; 39(6): 573–580.
  42. Chiu M, Rezai MR, Maclagan LC et al. Moving to a highly walkable neighborhood and incidence of hypertension: A propensity-score matched cohort study. *Environ Health Perspect* 2016 June; 124(6): 754–760.
  43. Kaiser P, Diez Roux AV, Mujahid M et al. Neighborhood environments and incident hypertension in the multi-ethnic study of atherosclerosis. *Am J Epidemiol* 2016 June; 183(11): 988–997.
  44. Mulatu MS, Schooler C. Causal connections between socioeconomic status and health: Reciprocal effects and mediating mechanisms. *J Health Soc Behav* 2002 March; 43(1): 22–41.

# Section II

## Etiological and Pathophysiological Aspects

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# HEMODYNAMIC PATTERNS IN HYPERTENSION

# 6

*Per Omvik and Per Lund-Johansen*

## INTRODUCTION

The flow of blood through the vascular system requires a driving force expressed as hydrostatic pressure – the blood pressure (BP). The level of BP is determined by the volume of blood expelled from the heart into the aorta per time unit – the cardiac output (CO), and the resistance against blood flow through the entire arterial system – the total peripheral resistance (TPR). Thus, BP may be expressed as the product of CO and TPR, or:

$$BP \approx CO \cdot TPR \quad (6.1)$$

Since CO is the product of stroke volume (SV) and heart rate (HR), Equation 6.1 may be rewritten:

$$BP \approx SV \cdot HR \cdot TPR \quad (6.2)$$

This may be termed the central hemodynamic equation. Any changes in BP, acute or chronic, involve change(s) in one or more of the three components on the right side of the equation, each of which are influenced by the interplay of a great many nervous, cardiac, vascular, renal, hormonal, humoral and genetic factors extensively described elsewhere in this book. This chapter discusses the effects of age, gender, dynamic exercise and antihypertensive treatment on the relationship between SV, HR, TPR and BP – the hemodynamic pattern – in hypertension.

## METHODS OF CENTRAL HEMODYNAMIC MEASUREMENTS

It is essential for clinical hemodynamic assessment to acquire accurate BP and CO measurements.

The most precise measurement of BP is obtained by intra-arterial recording using a pressure transducer, which permits detection of immediate beat-by-beat pressure changes, for example, during variations in physical activity or by other interventions (1). Intra-arterial recordings may also be carried out at different sites within the arterial

tree to obtain hemodynamic information from specific segments of the vascular system.

CO may be measured invasively by the Fick method, thermodilution, and dye dilution (2,3). CO is also measured noninvasively by methods like echocardiography and magnetic resonance imaging. While noninvasive techniques are easily available, the invasive techniques are considered the most accurate for measurement of CO (4–6). Advantages of the dye dilution technique using Cardiogreen® (indocyanine) are its usefulness both at rest and during exercise, and that measurement can be performed when patients are unrestricted, without knowing when the measurements are actually being performed. Hence reflex effects due to anticipation are at a minimal level. The repeatability is in the order of 5%, and dye dilution has been termed the gold standard (2,6). Limitations are that the technique is invasive and gives the mean value over 10–30 s (not beat-to-beat values).

By most methods, the CO is measured as volume per time unit, usually L/min. CO may in turn be used to calculate the SV when HR is known (preferably by electrocardiogram):

$$SV = CO/HR \quad (6.3)$$

By noninvasive techniques the situation is reversed: the SV is the variable being measured and the CO is then obtained by the calculation:

$$CO = SV \times HR \quad (6.4)$$

TPR cannot be measured directly, but is derived by calculation as the ratio between the mean arterial pressure (MAP) and CO:

$$TPR \approx MAP/CO \quad (6.5)$$

The TPR in Equation 6.5 is usually transformed by a constant (1332) to be expressed by the unit  $\text{dyn s cm}^{-5}$ . Indexed values for TPR, as well as for CO and SV, are obtained by relating data to body surface area (BSA). The corresponding variables are designated cardiac index (CI),

stroke index (SI), and total peripheral resistance index (TPRI). Indexed hemodynamic variables allow comparison of results between different trial populations and between different laboratories.

According to Poiseuille's law, vascular resistance is determined by blood viscosity, and length and diameter of the resistance vessels, with the arteriolar diameter as the dominant factor. As discussed by Folkow, even minute changes in diameter may cause large differences in resistance (7). By an ingenious technique with determination of small artery structure in terms of media-to-lumen ratio, it has been possible to directly study factors that may be of importance in the control of arteriolar diameter (8). By this technique it has been possible to show a link between structural alterations in the microvasculature and aortic stiffness (9).

## HEMODYNAMIC PATTERN IN NORMOTENSION

Invasive hemodynamic measurements in healthy, normotensive individuals have been carried out only in a limited number of small-scale studies, mostly in men aged 20–40 years (1,10–15). The total number of individuals in these studies is approximately 200. The weighted mean values of the hemodynamic variables in the rest supine position from these studies are shown in Table 6.1.

## AGE

In normotensive subjects between the ages 18–50 years, hemodynamic data from cross-sectional studies are rather similar in young and older age groups. Age-related changes in central hemodynamic variables from cross-sectional studies in normotensive and hypertensive subjects from our laboratory from the 1960s are shown in Figure 6.1 (1).

Few studies on the spontaneously occurring changes in central hemodynamics over time have been published. In a 5-year follow-up study from Sweden in young men there were virtually no changes in BP, HR, CO or TPR, which is in agreement with the cross-sectional data from our laboratory (1,15).

**Table 6.1** Central hemodynamics at rest supine in NT subjects

|                                             |      |
|---------------------------------------------|------|
| MAP <sup>a</sup> ; mmHg                     | 85.6 |
| CI; L/min/m <sup>2</sup>                    | 3.30 |
| TPRI; dyn s cm <sup>-5</sup> m <sup>2</sup> | 2118 |
| HR; beats/min                               | 66.7 |
| SI; mL/stroke/m <sup>2</sup>                | 51.1 |

Note: Mean values from seven studies.

<sup>a</sup> MAP = DAP + 1/3(SAP – DAP). In invasive studies, MAP is obtained by electrical damping of the intra-arterial pressure curve (1).

Abbreviations: CI, cardiac index; DAP, diastolic arterial pressure; HR, heart rate; MAP, mean arterial pressure; NT, normotensive; SAP, systolic arterial pressure; SI, stroke index; TPRI, total peripheral resistance index.

## EXERCISE

During extreme muscular exercise CO is increased by 300% or more. The distribution of blood flow in the body is dramatically changed – mainly by a large increase in the proportion of blood flow to working muscles, including the myocardium. While hemodynamic disturbances at rest in mild hypertension or in cardiac disease may be small, such changes are more clearly unveiled during exercise – when the circulatory system is really challenged. Thus hemodynamic responses to exercise are often used in clinical practice for evaluation of cardiac pump function. However, systematic exercise hemodynamic studies in healthy, normotensive subjects using invasive techniques are scarce. In a study of 33 normotensive men aged 19–49 years (mean 31) from our laboratory, there was an increase in systolic arterial pressure (SAP) of 34.3 mmHg at a steady-state dynamic (bicycle) workload of 100 W compared to the rest (sitting) situation (1). The corresponding increase in diastolic arterial pressure (DAP) was 3.8 mmHg, in CI 6.0 L/min/m<sup>2</sup>, in SI 28.4 mL/stroke/m<sup>2</sup>, and in HR 53 beats/min. The TPRI fell by 1308 dyn s cm<sup>-5</sup> m<sup>2</sup> (Figure 6.2).

## HEMODYNAMIC PATTERNS IN HYPERTENSION

In nearly all the studies performed in middle-aged subjects with established, uncomplicated hypertension, the CO during rest has been normal or slightly reduced. The TPR has been increased, referred to as the 'hallmark of hypertension' (2). The resistance has also been found increased in all vascular beds (cerebral, renal, myocardial, pulmonary, splanchnic, muscular and skin) in clinical as well as in experimental hypertension (16–24).

In young men (18–30 years) with BP above 140/90 mmHg, invasive studies have shown an increase in CO of about 15% compared with age-matched normotensive controls due to increased HR (10–15%) and normal SV. The mean values of the seven available studies are shown in Figure 6.3 (1,10–15). These hemodynamic changes are thought to be due to sympathetic nervous system hyperactivity, which has been linked to the starting phase of essential hypertension (25,26).

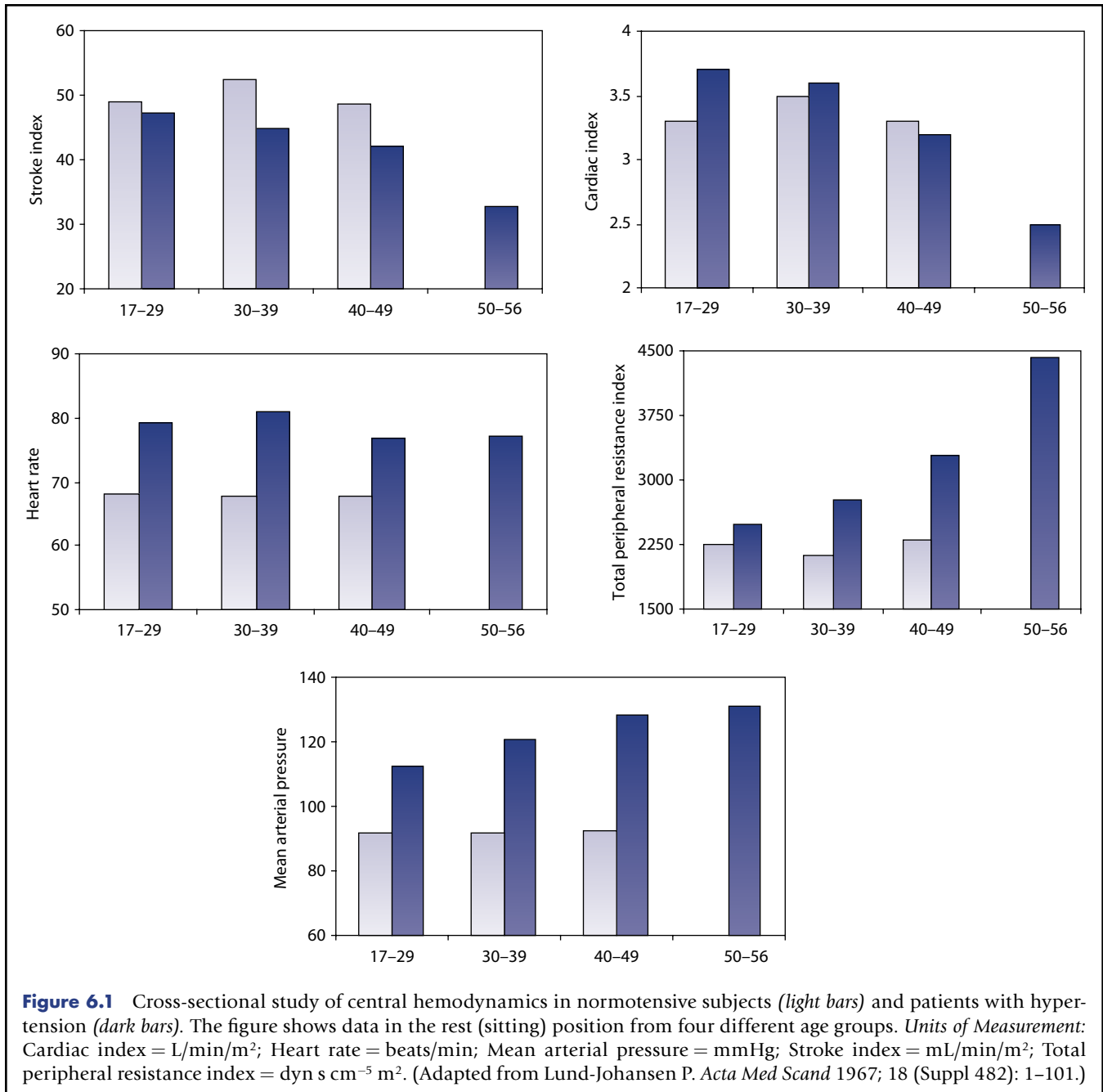
## AGE

### CROSS-SECTIONAL STUDIES

The age-related increase in BP in hypertensive subjects is due to a progressive increase in TPR, which at the age of 50 may be almost twice the value seen at the age of 20 (Figure 6.1). In young hypertensives the resting CO is often increased by 15–20% compared with normotensive subjects. Thereafter, CO progressively declines with age, associated with reduction in SV, while HR remains increased 6–10 beats/min up to the age of 50–60 years.

The true nature of the reduction in cardiac pump function with age seen in hypertension is not readily apparent. In a group of offspring (mean age 40) from parents, who at a national health screening 27 years earlier had a BP above 140/90 mmHg, an increased relative wall thickness and a shift of left ventricular diastolic filling from early to late diastole was seen when compared to offspring from parents





who were normotensive both at the screening and at the time of the current study (Table 6.2) (27). Similar findings have been made in other studies, suggesting increased left ventricular stiffness and reduced ventricular filling rate even before development of left ventricular hypertrophy (28-31).

### LONGITUDINAL STUDIES

Available follow-up studies on spontaneous changes in central hemodynamics in hypertensives are of short duration – typically 2-5 years (3,15,32-38). Generally, BP remained unchanged, while the CO decreased, and TPR showed an increase. In our laboratory similar results were found after a 10-year follow-up period (32,38). The reduction in CO was associated with a reduction in SV in the order of 15%, while HR was almost unchanged. Thus, the progressive decrease

in cardiac pump function with age in hypertensives as suggested from the cross-sectional studies is also seen by longitudinal follow-up in individual patients.

In our laboratory a second restudy after a total of 20 years from the first hemodynamic study was performed in a limited group of patients (32,33,38). During the second decade, most patients developed diastolic BP above 100 mmHg, and active antihypertensive treatment was initiated in all but two patients. After consent from the patients, and under close scrutiny, the drug therapy was temporarily discontinued for 1 month in order to evaluate the hemodynamic status without drug effects after 20 years of follow-up. The principal results were further increases in systolic and diastolic BPs associated with increase in TPR and further reductions in CO and SV (Figure 6.2) (33).

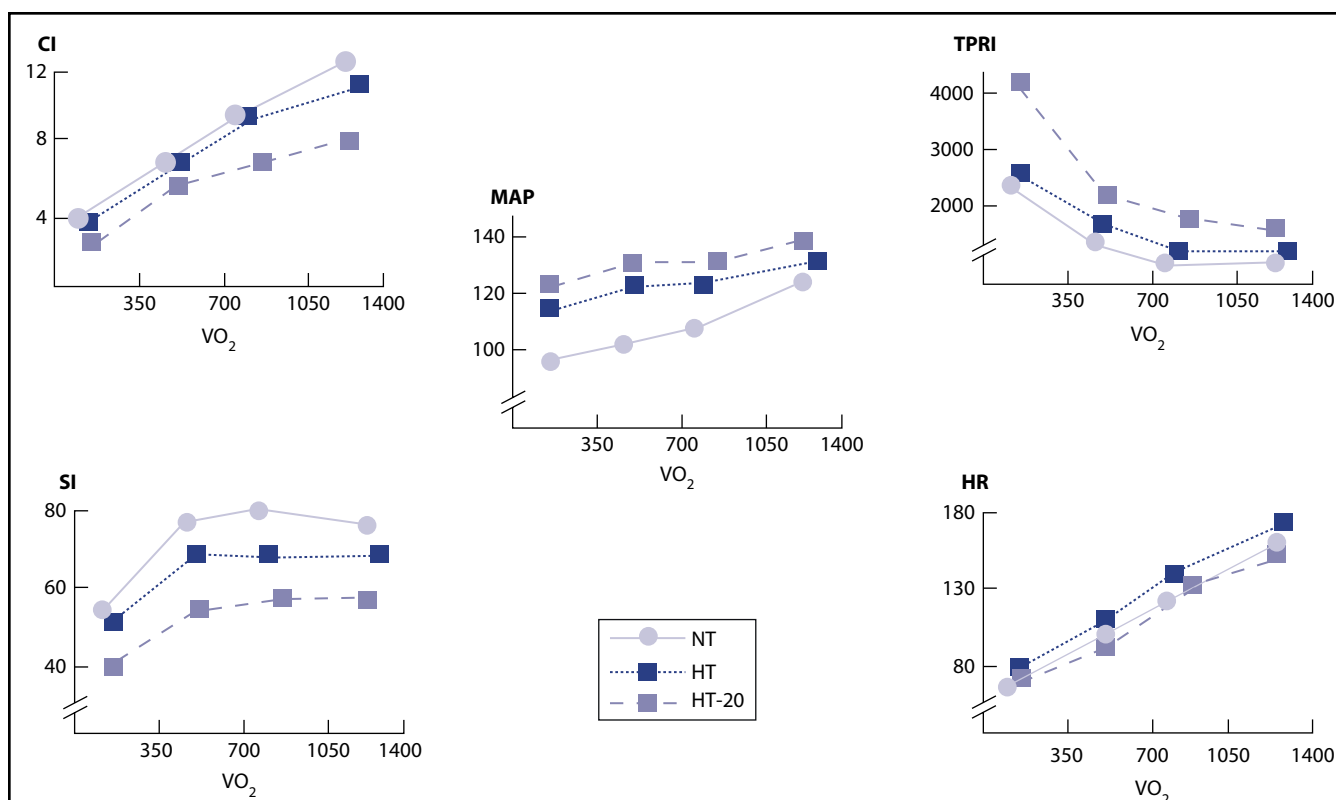


**Figure 6.2** Central hemodynamics in young hypertensive (HT) men and in the same subjects 20 years later (HT-20) in comparison with age-matched normotensive (NT) controls. Data shown at the lowest oxygen consumption ( $VO_2$ ) values represent measurements at rest sitting, while the remaining data show measurements during steady state dynamic exercise at 50, 100 and 150 W, respectively. Abbreviations: CI, cardiac index (L/min/m<sup>2</sup>); HR, heart rate (beats/min); MAP, mean arterial pressure (mmHg); SI, stroke index (mL/beat/m<sup>2</sup>); TPRI, total peripheral resistance index (dyn sec cm<sup>-5</sup> m<sup>2</sup>);  $VO_2$ , oxygen consumption (mL/min/m<sup>2</sup>), measured by the Douglas bag technique. (From Lund-Johansen P. *Acta Med Scand* 1967; 18(Suppl 482): 1–101; Lund-Johansen P. In: Birkenhäger WH, Reid JL (eds). *Handbook of Hypertension*, vol 22. Birkenhäger WH, Robertson JIS, Zanchetti A (eds). *Hypertension in the Twentieth Century: Concepts and Achievements*. Elsevier, Amsterdam; 2004:151–72; Lund-Johansen P. *Hypertension* 1991; 18(Suppl): III-54–III-61.)

## EXERCISE

Several comparative studies on the circulatory system during exercise between patients with hypertension and normal age-matched controls have been carried out in the past (1,39–42). In subjects between 17 and 49 years of age with mild or borderline hypertension, the increase in BP during ergometer bicycling with increasing loads was parallel to what was seen in the normotensive controls.

Surprisingly, the SV did not increase to the same levels during exercise in patients with hypertension as in normotensive controls (1). In patients with hypertension the SI was approximately 15% lower than in normal controls during all exercise levels (50, 100 and 150 W). The increase in SI from rest to 100-Watt (W) steady-state exercise was 20.4 mL/stroke/m<sup>2</sup> as compared with 28.4 mL/stroke/m<sup>2</sup> in the normotensive subjects. Thus, during exercise the CI was no longer higher than in normotensive controls, but actually significantly subnormal, particularly during strenuous exercise (150 W). The oxygen consumption was

similar, and as a consequence, the arteriovenous oxygen difference [(A-V) $O_2$ ] was increased.

Patients with really severe hypertension but without clinical symptoms of heart failure had markedly reduced CI compared to normotensive controls (43). In transition from moderate to severe exercise, SI actually decreased. These findings could be interpreted as an indication of incipient cardiac failure (1). Other studies have shown that in relation to the filling pressure, CI is reduced in patients with severe hypertension (42). TPR was numerically normal during rest in the youngest group but was significantly higher than normal during exercise at all exercise levels. In older age groups the TPR was increased also at rest (Figure 6.1).

The most important conclusions from the exercise studies are that cardiac pump function and vessel resistance are affected very early in subjects with mild, uncomplicated essential hypertension. One mechanism is reduced compliance of the left ventricular wall (44–46). Studies of heart pump function by echo-Doppler method in subjects with very mild hypertension have revealed a slight degree of left ventricular hypertrophy and diastolic dysfunction, characterized by reduction in the E/A ratio. This indicates

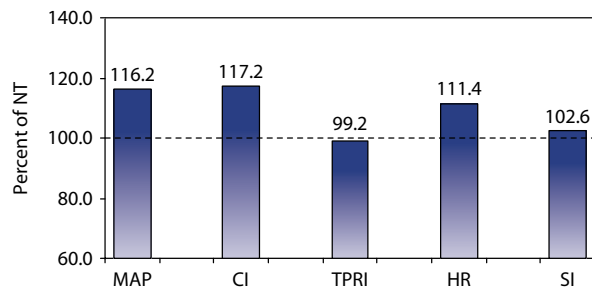


**Figure 6.3** Central hemodynamic variables in young subjects with mild essential hypertension. Data are shown as percent compared with normotensive (NT) subjects (dashed line = 100%) and are the weighted mean values for the supine position at rest from seven studies in a total of 189 NT subjects and 222 patients with essential hypertension. Abbreviations: CI, cardiac index; HR, heart rate; MAP, mean arterial pressure; SI, stroke index; TPRI, total peripheral resistance index. (From Lund-Johansen P. *Acta Med Scand* 1967; 181(Suppl 482): 1–101; Bello CT et al. *Am J Med Sci* 1967; 253: 194–208; Frohlich ED et al. *Am J Med Sci* 1969; 257: 9–23; Safar M et al. *La Presse Medicale* 1970; 78: 111–4; Julius S et al. *Circulation* 1971; 43: 382–90; Jern S. *Acta Med Scand Suppl* 1982; 662: 1–55; Andersson OK et al. *J Hypertens* 1983; 1(Suppl 2): 91–93. (10,19–24))

that the filling of the left ventricle is slightly reduced and more dependent on the atrial contraction in hypertension than in normal subjects.

Muscular exercise increases the workload on the heart and the myocardial oxygen need. The product of  $HR \times SAP$  (the rate – pressure product [RPP]) is a clinically useful index of myocardial oxygen demand (47). When the RPP is compared in hypertensives and normotensive subjects

**Table 6.2** Pre-hypertensive changes in offspring of hypertensive families

|                                      | Offspring of normotensive families (n = 47) | Offspring of hypertensive families (n = 41) |
|--------------------------------------|---------------------------------------------|---------------------------------------------|
| Age (y)                              | 33                                          | 40***                                       |
| Body mass index (kg/m <sup>2</sup> ) | 24.1                                        | 24.4                                        |
| Office BP (mmHg)                     | 117/68                                      | 135/83***                                   |
| 24-hour ambulatory BP (mmHg)         | 112/65                                      | 122/74***                                   |
| Office HR (beats/min)                | 69                                          | 76**                                        |
| 24-hour ambulatory HR (beats/min)    | 70                                          | 76*                                         |
| Posterior wall thickness (mm)        | 9.3                                         | 10.1*                                       |
| Relative wall thickness              | 0.36                                        | 0.41***                                     |
| Peak late flow (m/s)                 | 0.42                                        | 0.52***                                     |
| Early/late flow (ratio)              | 1.72                                        | 1.41***                                     |

Source: Mo R et al. *Blood Pressure* 1995; 4: 16–22.

Note: The Bergen Blood Pressure Study; Statistical difference between offspring of normotensive and hypertensive families: \* =  $p < 0.05$ ; \*\* =  $p < 0.01$ ; \*\*\* =  $p < 0.001$ .

of similar age, it is seen that during rest in the hypertensive groups, the RPP is similar to what normotensives are exposed to during 50 W exercise (Figure 6.4) (48). This illustrates the chronic increased burden on the hypertensive heart – also at rest.

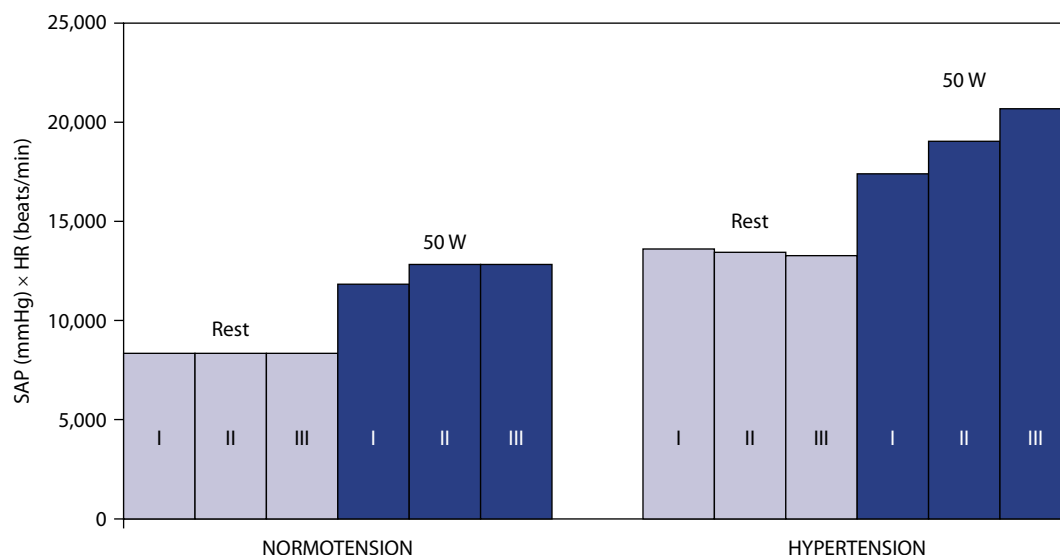


**Figure 6.4** The systolic arterial pressure-heart rate product ( $SAP \times HR$ ) at rest (solid bars) and during steady state 50 W bicycle exercise (open bars) in normotensive subjects and hypertensive patients in three age groups: I = 18–29 years; II = 30–39 years; III = 40–49 years. (From Lund-Johansen P. *Eur Heart J* 1999; 1(Suppl B): B10–B17.)

## GENDER

Differences in hemodynamic patterns between males and females have been shown in the past by noninvasive techniques, but to our knowledge systematic studies of central hemodynamics using invasive methods have neither been performed in normotensive women nor in women with hypertension (49,50). In our laboratory more than 500 individuals have participated in invasive hemodynamic studies. About 10% were women. In an attempt to elucidate possible differences in the hemodynamic patterns in untreated hypertensive men and women, a post hoc analysis was performed in which hemodynamic data from 57 women were compared with data from 57 men who were matched with respect to age and systolic, diastolic, and mean arterial pressure at rest in the sitting position. Body mass index (BMI) was almost the same in the two groups, 25.7 versus 25.1 kg/m<sup>2</sup>. The main finding was a similar hemodynamic pattern in hypertensive men and women at rest, while during exercise arterial pressure and HR increased more sharply in women (Table 6.3, unpublished data). At rest the SI was almost the same in the two groups, but during exercise SI increased less (30%) in women than in men. Thus, with higher HR and lower SI in women, the CI did not differ significantly between the two genders

during exercise (Figure 6.5). TPRI tended to be slightly higher (4–7%) in women than in men, but this difference did not reach statistical significance.

One implication of higher arterial pressure and HR in women with hypertension during exercise was a larger increase in RPP than in men. From Figure 6.6 it may be seen that at 50-W exercise the mean RPP in the female group was about the same as in the male group at 100 W, and similarly, the RPP in women at 100 W was the same as at 150 W in men.

The RPP increases with age (51). By dividing the male and female groups into 'young' and 'old' halves (males, mean age 36.7 and 55.0 y, and females 36.4 and 55.5 y, respectively), the 'young' female group showed the same profile of RPP with increasing exercise as the 'old' men group. An additional hemodynamic difference between the two genders was that females had higher pulse pressure/stroke volume index (PP/SI; a surrogate index of arterial stiffness) that became statistically significant during exercise. Recently it has been shown that hypertension is a more important cardiovascular (CV) risk factor in women than in men (52–55).

## HEMODYNAMIC PATTERNS DURING ANTIHYPERTENSIVE THERAPY

Changes in the hemodynamic pattern during antihypertensive therapy may be used to study the mechanisms of action of the antihypertensive agents (56,57), and conversely, pharmacological challenging of hemodynamic variables may expose underlying hemodynamic mechanisms of hypertension and thus serve as tools to investigate the pathophysiology of the disease. Tables 6.4 and 6.5 show the overall data from 37 invasive studies in our laboratory on central hemodynamic changes at rest and during steady-state exercise at 100 W induced by 1-year treatment by the major drug classes of antihypertensive drugs and also by low salt diet. Figure 6.7 depicts central hemodynamic variables at rest and during exercise before and after treatment with two different classes of antihypertensive agents: beta-blockers and non-dihydropyridine calcium channel blockers (CCBs). In addition, data from a group of normotensive subjects of similar age are shown for comparison. Details from all studies have been published elsewhere (58–90). In Tables 6.4 and 6.5, the drug classes are ranked according to the TPRI response at rest sitting.

## CALCIUM CHANNEL BLOCKERS

CCBs have the common property of interacting with L-type voltage-gated plasma membrane calcium channels. There are several subtypes of CCBs which from both a pharmacological and hemodynamic point of view may broadly be divided into *dihydropyridines* and *non-dihydropyridines* (91,92). Generally, all CCBs are vasodilators, reducing BP by a reduction of TPR.

However, the mechanisms by which CCBs reduce vascular resistance is complex, including both vasoconstrictor and vasodilator components. One mechanism is stimulation of renin release due to reduction in intracellular Ca<sup>2+</sup> (92). Another is inhibition of endothelin-I-induced

**Table 6.3** Hemodynamic variables in 57 women and 57 men with hypertension matched with respect to age, systolic, diastolic and mean arterial pressure in the rest sitting position

|                                               | Rest (sitting position) |         | Exercise (100 Watt) |          |
|-----------------------------------------------|-------------------------|---------|---------------------|----------|
|                                               | Males                   | Females | Males               | Females  |
| Age (y)                                       | 46.0                    | 46.8    |                     |          |
| SAP (mmHg)                                    | 179.6                   | 181.1   | 211.9               | 218.7    |
| DAP (mmHg)                                    | 105.4                   | 105.3   | 110.8               | 117.8*   |
| MAP (mmHg) <sup>a</sup>                       | 132.9                   | 133.6   | 151.3               | 162.7**  |
| HR (beats/min)                                | 74.9                    | 78.4    | 133.4               | 156.8*** |
| SI (mL/beat/m <sup>2</sup> )                  | 36.3                    | 33.5    | 51.3                | 43.0***  |
| CI (L/min/m <sup>2</sup> )                    | 2.68                    | 2.58    | 6.72                | 6.60     |
| TPRI (dyn s cm <sup>-5</sup> m <sup>2</sup> ) | 4215                    | 4365    | 1888                | 2017     |
| HR*SAP (mmHg*beats/min)                       | 13452                   | 14248   | 28520               | 34307*** |
| PP/SI (mmHg/mL/beat/m <sup>2</sup> )          | 2.17                    | 2.40    | 2.13                | 2.48*    |
| VO <sub>2</sub> (mL/min/m <sup>2</sup> )      | 168                     | 169     | 852                 | 972***   |

<sup>a</sup> MAP = DAP + 1/3(SAP – DAP). Mean arterial pressure (MAP) was obtained by electrical damping of the intra-arterial pressure curve (28). Abbreviations: SAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate; SI, stroke index; CI, cardiac index; TPRI, total peripheral resistance index; HR\*SAP, rate-pressure product; PP/SI, pulse pressure/stroke volume index; VO<sub>2</sub>, oxygen consumption (measured by the Douglas bag technique). Statistical significance of difference between males and females: \* p < 0.05; \*\* p < 0.01; \*\*\* p < 0.001.

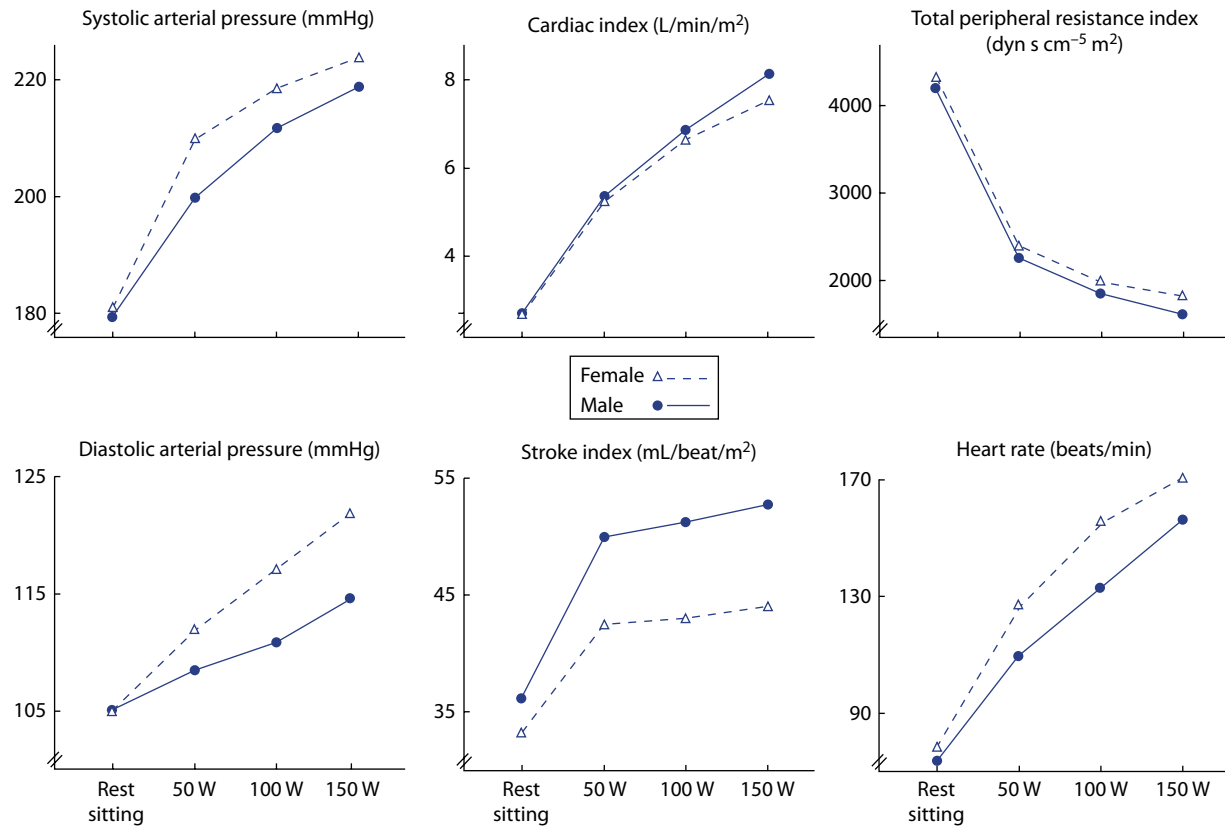


**Figure 6.5** Central hemodynamics at rest and during exercise in 57 women (triangles) with essential hypertension and 57 men (circles) with matching age, and systolic, diastolic and mean arterial pressure (at rest sitting). Abbreviations: CI, cardiac index; SI, stroke index; HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; TPRI, total peripheral resistance index.

vasoconstriction as shown by forearm venous occlusion plethysmography (93,94).

Acute administration of dihydropyridine CCBs is accompanied by a reflex increase in HR, and thereby an increase in CO which, in spite of a marked reduction in TPR, blunts the immediate hypotensive effect (74,95). After the initial rise, HR gradually levels off towards its usual level. The long-term antihypertensive response to CCBs is partly dependent on sympathetic reflex activation (95).

The central hemodynamic difference between dihydropyridine and non-dihydropyridine CCBs is related to different HR response. As shown in Tables 6.4 and 6.5, the main long-term hemodynamic difference between the two groups of CCBs is a small reduction in HR (about 5 beats/min; 6%) by non-dihydropyridines (Figure 6.7) as opposed to unaltered HR during dihydropyridine therapy. The negative chronotropic effect of non-dihydropyridines is compensated for by an increase in SV (at rest sitting 9.3%, Figure 6.7), leaving CO almost unchanged at rest and during exercise with both CCB groups.

## ALPHA RECEPTOR BLOCKERS

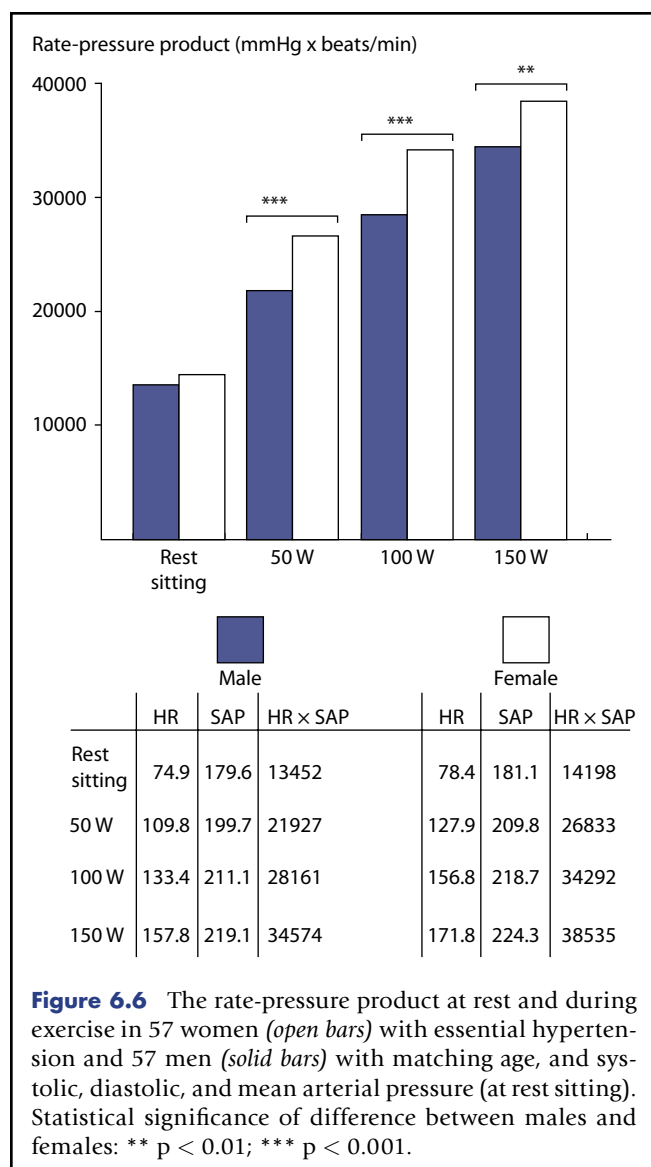
Postsynaptic alpha receptor blockers have in general been omitted from international recommendations on

antihypertensive treatment because of increased morbidity and mortality related to heart failure compared with other antihypertensive drugs in randomized clinical trials (96,97). Alpha receptor blockers are still included here because of interesting hemodynamic properties in patients with hypertension. As may be seen from Tables 6.4 and 6.5, compounds from this group (and ARBs) were the only 'true' vasodilators, in other words, compounds that at the same time led to significant reduction in TPR and increases in SV and CO without affecting HR at rest or during exercise. However, it should be noted that even though the hemodynamic profile approached normal after 1-year alpha receptor blockade, there was still a wide gap to fully normalizing central hemodynamics by alpha receptor blocker treatment.

## ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme inhibitors (ACEIs) slow down the conversion of angiotensin-1 to angiotensin-2 which, among other effects, is a strong stimulus for arteriolar vasoconstriction (Chapter 13). Modulation of the hemodynamic pattern by ACE inhibitors was studied in five trials: Captopril, enalapril, lisinopril + hydrochlorothiazide, lisinopril + low salt diet, and perindoprilat (acute, not long-term response) (43,78–80). The general





finding after 1-year treatment was a significant reduction in BP that was mainly due to reduction in TPR with minor changes in SV and CO. In some patients, in our study as well as in others, moderate sodium restriction or a thiazide diuretic was added, which enhanced (thiazide more than sodium restriction) the antihypertensive effect (13,14). The potentiation of blood pressure reduction with sodium restriction or a thiazide was expected, as both adjuvants are known stimulants of the renin-angiotensin system (98,99). Moreover, when a thiazide was added, both TPR and CO were reduced. The reduction in CO and MAP was associated with a significant reduction in extracellular fluid volume (79). The acute study with perindoprilat showed rather similar immediate hemodynamic changes as seen after 1-year ACE inhibitor treatment (80).

## ANGIOTENSIN RECEPTOR-1 BLOCKERS (ARBs)

Both clinical and experimental studies have shown that angiotensin receptor-1 blockade, in addition to inhibition

of the vasoconstrictor action of angiotensin II, is associated with a significant improvement in resistance vessel endothelial function, which conceivably might be expressed in terms of hemodynamic changes (101).

In a study of 8-month treatment with the ARB losartan in patients with essential hypertension, the hemodynamic response was mainly vasodilatation with a reduction in TPR and BP (90). There were almost no changes in CO or SV at rest, whereas during exercise a small increase was seen in SV (Tables 6.4 and 6.5). However, the TPR during ARB treatment was still above what was seen in normotensive subjects of the same age, and similarly, the SV and CO both at rest and during exercise was less than in the normotensive subjects (1). Thus, although the vasodilatation induced by angiotensin receptor-1 blockade tended to normalize the central hemodynamic disturbance of hypertension, full normalization was not achieved.

## DIURETICS

Thiazide diuretics were developed in the 1950s. In the early days, the compounds were administered in rather high doses which could lead to serious side effects, especially hypokalaemia. At a later stage, lower doses and longer dosing intervals became common and thiazides and thiazide-like diuretics were accepted as first-line antihypertensive treatment. In our laboratory the long-term hemodynamic effects of four compounds – chlorthalidone, polythiazide, hydrochlorothiazide and tienilinic acid – were studied in the late 1960s and 1970s (76,77).

The rationale for use of diuretics as antihypertensive treatment has been that they reduce body fluid volume, including blood volume, and thereby reduce left ventricular preload. Thus a reduction in CO was expected. Based on studies by Conway and others, it was once thought that the reduction in body fluid volumes with diuretics was a temporary phenomenon that gradually levelled off (101). However, as shown by Tarazi and co-workers, chronic thiazide therapy leads to persistent body fluid depletion and increased renin activity (99). In our experience, the hemodynamic profile after 8–12 months of diuretic treatment was characterized by a reduction in MAP caused by combined reduction in CO and TPR at rest. During exercise the reduction in MAP was almost entirely due to reduction in CO with chlorthalidone and by reduction in TPR with hydrochlorothiazide and polythiazide (76,77). Contrary to most other antihypertensive regimens, diuretic treatment led to larger relative reduction in SAP than DAP; about 19% versus 16%.

## DUAL (MULTIPLE)-ACTION DRUGS

This is a mixed group of drugs where the active compound has more than one effect on receptors controlling vascular tone, generally expressed by beta-blocking effect plus an additional vasodilating activity. One example is carvedilol, with  $\beta_1$ -,  $\beta_2$ -, and  $\alpha$ -receptor blocker properties, also termed a ‘vasodilating beta-blocker’ (83,102). The general hemodynamic profile of treatment with dual-action drugs is reduction in BP due to reduction in CO and either no increase, as seen with ‘pure’ beta-blockers, or, particularly during exercise, a limited reduction in TPR



**Table 6.4** One-year central hemodynamic changes (%) induced by different classes of antihypertensive drugs or low sodium diet

| Antihypertensive treatment group | Number<br>N = studies<br>n = patients | TPRI (4040 dyn<br>s cm <sup>-5</sup> m <sup>2</sup> ) <sup>a</sup> | MAP<br>(128,2 mmHg) | CI (2,65<br>L/min/m <sup>2</sup> ) | SI (36,5<br>mL/min/m <sup>2</sup> ) | HR (73,6<br>beats/min) |
|----------------------------------|---------------------------------------|--------------------------------------------------------------------|---------------------|------------------------------------|-------------------------------------|------------------------|
| CCB: Dihydropyridines            | N = 4; n = 65                         | -15.6                                                              | -14.3               | 4.3                                | 4.4                                 | -0.2                   |
| Alpha blockers                   | N = 3; n = 36                         | -14.9                                                              | -9.3                | 8.8                                | 8.4                                 | 1.1                    |
| CCB: Non-dihydropyridines        | N = 3; n = 41                         | -12.4                                                              | -11.9               | 2.6                                | 9.3                                 | -6.2                   |
| ACE inhibitors                   | N = 4; n = 65                         | -11.0                                                              | -16.5               | -3.7                               | -0.9                                | -2.6                   |
| ARB                              | N = 1; n = 30                         | -8.7                                                               | -8.3                | 2.3                                | 3.5                                 | -0.6                   |
| Diuretics                        | N = 4; n = 44                         | -7.0                                                               | -17.7               | -10.7                              | -11.3                               | 0.7                    |
| Dual-action drugs                | N = 4; n = 65                         | -1.8                                                               | -14.4               | -10                                | 2.1                                 | -11.7                  |
| Centrally acting                 | N = 3; n = 39                         | 1.6                                                                | -10.6               | -10.8                              | -1.7                                | -8.6                   |
| Low sodium diet                  | N = 3; n = 58                         | 10.6                                                               | -1.6                | -8.1                               | -5.1                                | -3.8                   |
| Beta-blockers                    | N = 8; n = 100                        | 11.5                                                               | -13.1               | -24.0                              | -2.9                                | -20.7                  |

Note: Observations at rest sitting.

<sup>a</sup> The data in parentheses show overall mean hemodynamic values before treatment in 542 patients with hypertension from 37 studies. CCBs are divided into dihydropyridines and non-dihydropyridines.

Abbreviations: CI, cardiac index; SI, stroke index; HR, heart rate; MAP, mean arterial pressure; CCB, calcium channel blockers; ACE, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor-1 blockers. The drug classes are ranked according to the TPRI response at rest sitting.

(Tables 6.4 and 6.5). The dual-action drugs reduce CO by reducing HR, but not to the same extent as beta-blockers without additional vasodilating effect. In the same manner as with beta-blockers, the reduction in HR during exercise is partly compensated for by an increase in SV. The

hemodynamic profiles seen after 1-year treatment with two compounds, labetalol and carvedilol, were maintained almost unchanged also after a 6-year treatment period (103). One of the compounds in this class, prazosin, has been withdrawn because of serious side effects.

**Table 6.5** One-year central hemodynamic changes (%) induced by different classes of antihypertensive drugs or low sodium diet

| Antihypertensive treatment group | Number<br>N = studies<br>n = patients | TPRI (1743 dyn<br>s cm <sup>-5</sup> m <sup>2</sup> ) <sup>a</sup> | MAP<br>(145,4 mmHg) | CI (6,87<br>L/min/m <sup>2</sup> ) | SI (53,0<br>mL/min/m <sup>2</sup> ) | HR (132,1<br>beats/min) |
|----------------------------------|---------------------------------------|--------------------------------------------------------------------|---------------------|------------------------------------|-------------------------------------|-------------------------|
| CCB: Dihydropyridines            | N = 4; n = 65                         | -10.8                                                              | -13.0               | -2.4                               | -0.8                                | -3.0                    |
| Alpha blockers                   | N = 3; n = 36                         | -13.7                                                              | -8.8                | 5.0                                | 4.7                                 | 0.2                     |
| CCB: Non-dihydropyridines        | N = 3; n = 41                         | -8.4                                                               | -10.1               | -2.4                               | 6.4                                 | -9.0                    |
| ACE inhibitors                   | N = 4; n = 65                         | -7.7                                                               | -12.9               | -5.7                               | -4.2                                | 0.3                     |
| ARB                              | N = 1; n = 30                         | -11.7                                                              | -7.4                | 7.5                                | 9.5                                 | -2.0                    |
| Diuretics                        | N = 4; n = 44                         | -7.5                                                               | -16.1               | -6.4                               | -5.0                                | -2.3                    |
| Dual-action drugs                | N = 4; n = 65                         | -5.1                                                               | -14.8               | -8.0                               | 7.2                                 | -14.5                   |
| Centrally acting                 | N = 3; n = 39                         | -3.3                                                               | -9.0                | -4.8                               | 0.9                                 | -5.3                    |
| Low-sodium diet                  | N = 3; n = 58                         | 1.1                                                                | -2.2                | -3.6                               | -0.2                                | -3.7                    |
| Beta-blockers                    | N = 8; n = 100                        | 6.2                                                                | -11.4               | -18.1                              | 5.2                                 | -21.7                   |

Note: Observations during 100 W dynamic exercise.

<sup>a</sup> The data in parentheses show overall mean hemodynamic values before treatment in 542 patients with hypertension from 37 studies. CCBs are divided into dihydropyridines and non-dihydropyridines.

Abbreviations: CI, cardiac index; SI, stroke index; HR, heart rate; MAP, mean arterial pressure; CCB, calcium channel blockers; ACE, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor-1 blockers. The drug classes are ranked according to the TPRI response at rest sitting.

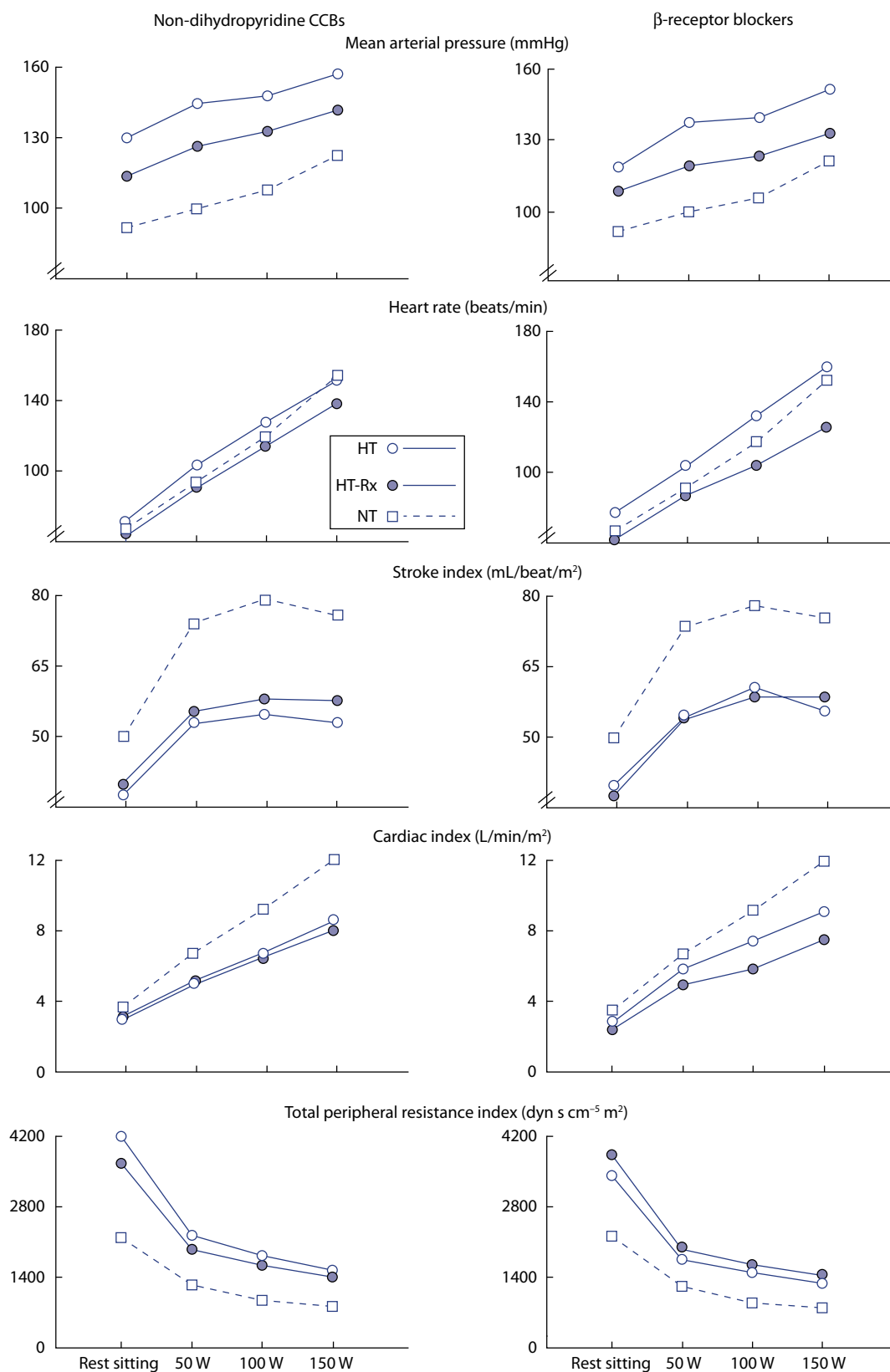


**Figure 6.7** Effects of one-year treatment with non-dihydropyridine CCBs (left hand panels) (69–71) or  $\beta$ -receptor blockers (right hand panels) (61–68) on central hemodynamics at rest and during exercise in patients with essential hypertension. Abbreviation: CCB = calcium channel blocker. Symbols: Open circles = before treatment; filled circles = same patients after one-year antihypertensive treatment; open squares = normotensive subjects. (Adapted from Lund-Johansen P. *Acta Med Scand* 1967; 18(Suppl 482): 1–101.)

## CENTRALLY ACTING DRUGS

Except for specific indications (alpha methyldopa: hypertension in pregnancy; clonidine: hypertensive crisis), this class of drugs has largely been dropped from general use in hypertension, mainly because of heavy cerebral side effects (89). The drugs exert their hypotensive effects by peripheral sympatho-inhibition via interference with alpha adrenoceptors and serotonergic pathways in the brain (104). In our studies, a moderate reduction in MAP (11 and 9% at rest and exercise, respectively) was observed, mainly caused by reduction in CO due to slowing of HR and almost unchanged TPR.

## LOW-SALT DIET

Salt (more precisely, sodium) has been proposed as an important etiological factor in hypertension. Thus conceptually it could be expected that reduction of salt intake might reduce BP by improving the cardinal hemodynamic disturbance of hypertension – an increase in TPR. However, invasive data from our laboratory showed that 6–9 months of salt restriction in patients with moderate essential hypertension was associated with a small reduction in MAP (on average 1.6% at rest and 2.2% during 100 W exercise) that was caused by a reduction in CO, while TPR actually increased (Tables 6.4 and 6.5) (85,86). The failure to normalize central hemodynamics might be due to the known stimulating effect of sodium deprivation on the renin-angiotensin system and the sympathetic nervous system and serve as a counterregulatory mechanism preventing excessive BP fall (98,99,105,106).

The modest antihypertensive effect of low-salt diet for 6–9 months in a limited number of patients seen in our studies was, as summarized by Graudal et al., corroborated in multiple randomized clinical trials including about 10,000 subjects between 1950 and 2016: in normotensive Caucasian subjects, the BP reduction after more than 4 weeks of low-salt diet was in the order of 1% and in hypertensive patients 3.5% (106).

One reason that has been put forward for modest overall BP response to reduced salt intake is salt sensitivity: some individuals respond more vigorously to changes in salt consumption than others. In our laboratory we examined the central hemodynamic profile in 37 hypertensive patients, 7 of whom were salt-sensitive and 30 salt-resistant (107). There were no statistically significant differences in BP, CO or TPR between the two groups at rest or during 100 W exercise. In another group of hypertensives, the status of salt sensitivity was tested in exactly the same way on two different occasions 2 months apart (108). When 24-h ambulatory BP measurement was used as criterion, only 60% of the patients had the same salt-sensitivity status (i.e. either salt-sensitive or salt-resistant) on both occasions, and 53% maintained their status when casual BP measurement was used.

The above findings reduce the likelihood that salt is a major etiological factor in the development of hypertension. The wider question whether salt is of importance in relation to CV disease events and mortality has been debated for a century, and still is. In a recent pooled analysis of 133,118 individuals from 49 countries in 4 prospective studies, Mente et al. found no increase in CV risk

at the high end of sodium excretion ( $>7$  g/d) in people with normal BP, while the CV risk was increased (hazard ratio 1.26) at the lower end (sodium excretion  $<3$  g/d). In patients with hypertension the CV risk was increased at both the low and high ends (hazard ratio 1.34 and 1.23, respectively) (109).

## BETA-BLOCKERS

Since their introduction, it has been known that beta-blockers reduce HR and CO. As a consequence of the CO reduction, the BP is reduced as well, but because of an increase in TPR, the relative reduction in BP is less than that in CO.

Several beta-blockers are available with different properties with regard to the balance between  $\beta_1$  and  $\beta_2$  receptor blocking activity and to intrinsic sympathomimetic action (ISA). In Figure 6.7 and Tables 6.4 and 6.5, data from eight studies, three with selective  $\beta_1$  and five with nonselective  $\beta_{1+2}$  blockers, are included. Except for a difference in the changes at rest in SI between the selective- and the nonselective beta-blocker groups (1,4% vs.  $-5,8\%$ ;  $p < 0.05$ ), there were no statistically significant differences in the hemodynamic changes after 1-year treatment by the two groups of drugs. Some beta-blockers have also been designed with additional vasodilating properties – so-called ‘dual-action’ drugs (81–84).

It was once thought that the increase in TPR during beta-blockade was a temporary counterregulatory response and that with time chronic beta-blocker therapy would even reduce the TPR and the initial reduction in CO would be abolished. An overshoot of TPR and a distinct fall in CO after the first administration of a beta-blocker is indeed found, but as exemplified by 1-year and 5-year follow-up studies on the hemodynamic effects of atenolol from our laboratory, the main finding of reduced HR and CO and increased TPR is maintained also after 1- and 5-year beta-blocker treatment (61,110). Similar observations were made also after 5-year treatment with the combined  $\beta_{1+2}$ /alpha receptor antagonist labetalol and carvedilol (103).

## OVERVIEW

The above summary of hemodynamic patterns brought about by different antihypertensive drug regimens shows that the CCBs, the alpha blockers, and the drugs inhibiting the renin-angiotensin system are vasodilators that not only reduce TPR, but in some cases also increase SI and CO. All of these changes, in addition to lowering BP, are shifts in the right direction to normalizing central hemodynamics in hypertension, but for none of these drug groups full hemodynamic normalization is achieved.

At the other end of the scale, beta-blockers and low-salt diet increase the TPR, which in hypertensives is already increased from the starting point, by more than 10%. Due to the marked bradycardia induced by the beta-blockers, the CO, which is reduced in patients with hypertension, is further lowered by almost one quarter. Thus the BP is reduced despite marked increase in TPR. In the case of low-salt diet, CO is reduced more moderately, almost exactly opposing the increase in TPR, and hence the net effect on BP becomes modest.

## CONCLUSION

Hypertension is a hemodynamic disorder with a pattern varying from high CO and normal TPR in young age and early hypertension to a normal-to-low CO and high TPR in more established hypertension (32). An early sign of impairment of cardiac pump function in hypertension is most readily seen in SV, particularly during exercise. Offspring from families in which both parents are hypertensives show echocardiographic signs of increased left ventricular stiffness, even without actually being hypertensive.

The modern selection of antihypertensive agents offers the possibility to modulate the central hemodynamic pattern of hypertension, ranging from decrease in BP due to marked reduction in CO, which is partly counteracted by some increase in TPR, to vasodilatation with reduction in TPR, and in some cases a small increase in CO. The CO can be reduced or increased by changes in HR and/or SV. Sometimes a change in one of these variables may be balanced by an inverse change in the other, leaving CO unaltered.

It has been pointed out that vasodilatation, not hypotension, improves resistance vessel design during treatment of essential hypertension (111,112) and that 'de-stiffening' will be the future goal of antihypertensive treatment (113). Ideally, a perfect antihypertensive agent, in addition to being without metabolic and subjective side effects, should be able to reduce BP to normal levels by reducing TPR, restoring normal cardiac pump function both at rest and during exercise, and also reducing cardiac and arterial stiffness and thereby development of isolated systolic hypertension.

Some of the large randomized antihypertensive drug trials have shown that ACEIs and ARBs may reduce left ventricular hypertrophy more efficiently than other antihypertensive agents, and also that development of congestive heart failure – as well as other clinical endpoints – is more reduced when compared with other drugs (114). However, full normalization of left ventricular geometry is usually not seen (115). It is unknown whether this observation and the gap between normal and on-drug central hemodynamic pattern in patients with hypertension is linked, but from a hemodynamic point of view it is obvious that there is still a great potential for improvement in the modes of antihypertensive treatment.

## REFERENCES

- Lund-Johansen P. Hemodynamics in early essential hypertension. *Acta Med Scand* 1967; 181(Suppl 482): 1–101.
- Robertson I, Birkenhager WH, (eds). Cardiac output measurement. *Eur Heart J* 1990; 11(Suppl 1): 1–153.
- Truijten J, van Lieshout JJ, Wesselink WA, Westerhof BE. Noninvasive continuous hemodynamic monitoring. *J Clin Monit Comput* 2012; 26: 267–278.
- Brod J, Fencel V, Hejl Z, Jirka J, Ulrych M. General and regional hemodynamic pattern underlying essential hypertension. *Clin Sci* 1962; 23: 339–349.
- Conway J. Clinical assessment of cardiac output. *Eur Heart J* 1990; 11(Suppl 1): 148–150.
- Lund-Johansen P. The dye dilution method for measurement of cardiac output. *Eur Heart J* 1990; 11(Suppl 1): 6–12.
- Folkow B. Physiological aspects of primary hypertension. *Physiol Rev* 1982; 62: 347–504.
- Mulvany MJ, Aalekjaer C. Structure and function of small arteries. *Physiol Rev* 1990; 4: 922–962.
- Muiesan ML, Salvetti M, Rizzoni D et al. Pulsatile hemodynamics and microcirculation. Evidence for a close relationship in hypertensive patients. *Hypertension* 2013; 61: 130–136.
- Bello CT, Sevy RW, Harakel C. Relationship between clinical severity of disease and hemodynamic patterns in essential hypertension. *Am J Med Sci* 1967; 253: 194–208.
- Frohlich ED, Tarazi RC, Dustan HP. Re-examination of the hemodynamics of hypertension. *Am J Med Sci* 1969; 257: 9–23.
- Safar M, Fendler JP, Weil B et al. [Hemodynamic study of labile arterial hypertension] Etude hemodynamique de l'hypertension arterielle labile. [Article in French] *Press Med* 1970; 78: 111–114.
- Julius S, Pascual AV, Sannerstedt R, Mitchell C. Relationship between cardiac output and peripheral resistance in borderline hypertension. *Circulation* 1971; 43: 382–390.
- Jern S. Psychological and hemodynamic factors in borderline hypertension. *Acta Med Scand Suppl* 1982; 662: 1–55.
- Andersson OK, Sannerstedt R, Beckman M. Essential hypertension—implications for pathogenesis from repeated hemodynamic investigations in young men with elevated blood pressure. *J Hypertens* 1983; 1(Suppl 2): 91–93.
- Frohlich ED. Hemodynamic differences between black patients and white patients with essential hypertension. State of the art lecture. *Hypertension* 1990; 15(Pt 2): 675–680.
- Messerli FH, DeCarvalho JGR, Christie B, Frohlich ED. Systemic and regional hemodynamics in low, normal and high cardiac output borderline hypertension. *Circulation* 1978; 58: 441–448.
- Ferlinz J. Right ventricular performance in essential hypertension. *Circulation* 1980; 61: 156–162.
- Conway J. A vascular abnormality in hypertension. A study of blood flow in the forearm. *Circulation* 1963; 4(Pt 1): 520–529.
- Widimsky J, Jandova R, Ressel J. Pulmonary circulation in juvenile hypertension. *Cor Vasa* 1980; 22: 156–167.
- Strauer BE, Schwartzkopff B, Motz W. Coronary vascular changes in the progression and regression of hypertensive heart disease. *J Cardiovasc Pharmacol* 1991; 18(Suppl 3): S20–S27.
- O'Gorman DJ, Sheridan DJ. Abnormalities of the coronary circulation associated with left ventricular hypertrophy. *Clin Sci* 1991; 81: 703–713.
- Granstam SO, Granstam E, Fellstrom B, Lind L. Regional hemodynamic differences between normotensive and spontaneously hypertensive rats: A microsphere study. *Physiol Res* 1998; 47: 9–15.
- Strandgaard S, Olesen J, Skinhoj E, Lassen NA. Autoregulation of brain circulation in severe arterial hypertension. *Br Med J* 1973; 1(5852): 507–510.
- Esler M. Looking at the sympathetic nervous system as a primary source. In: Birkenhager WH, Reid JL (eds) *Handbook of Hypertension*. Vol 22. Birkenhager WH, Robertson JIS, Zanchetti A (eds). *Hypertension in the Twentieth Century: Concepts and Achievements*. Elsevier, Amsterdam; 2004:81–102.
- Julius S. Autonomic nervous system dysregulation in human hypertension. *Am J Cardiol* 1991; 67: 3B–7B.
- Zahka KG, Neill CA, Kidd L et al. Cardiac involvement in adolescent hypertension. Echocardiographic determination of myocardial hypertrophy. *Hypertension* 1981; 3: 664–668.
- Mo R, Nordrehaug JE, Omvik P, Lund-Johansen P. The Bergen Blood Pressure Study: Prehypertensive changes in cardiac structure and function in offspring of hypertensive families. *Blood Press* 1995; 4:16–22.
- Giannattasio C, Cattaneo BM, Mangoni AA et al. Cardiac and vascular structural changes in normotensive subjects with parental hypertension. *J Hypertens* 1995; 13: 259–264.
- Meetha SK, Super DM, Anderson RL et al. Parental hypertension and cardiac alterations in normotensive children and adolescents. *Am Heart J* 1996; 131: 81–88.
- Agabiti-Rosei E, Muiesan ML. Hypertension and the heart: From left ventricular hypertrophy to ischemia to congestive heart failure. In: Birkenhager WH, Reid JL (eds) *Handbook of Hypertension*. Vol 22. Birkenhager WH, Robertson JIS, Zanchetti A (eds). *Hypertension in the Twentieth Century: Concepts and Achievements*. Elsevier, Amsterdam; 1995:339–366.
- Lund-Johansen P. Hemodynamic concepts of hypertension: Cardiac output versus peripheral vascular resistance. In: Birkenhager WH, Reid JL (eds) *Handbook of Hypertension*. Vol 22. Birkenhager WH, Robertson JIS, Zanchetti A (eds). *Hypertension in the Twentieth Century: Concepts and Achievements*. Elsevier, Amsterdam; 2004:151–172.
- Lund-Johansen P. Twenty-year follow-up of hemodynamics in essential hypertension during rest and exercise. *Hypertension* 1991; 18(Suppl): III-54–III-61.



34. Eich RH, Cuddy RP, Smulyan H, Lyons RH. Hemodynamics in labile hypertension. A follow-up study. *Circulation* 1966; 34: 299–307.
35. Birkenhäger WH, Schalekamp MA, Krauss XH et al. Consecutive hemodynamic patterns in essential hypertension. *Lancet* 1972; 1(7750): 560–564.
36. Birkenhäger WH, de Leeuw PW. Cardiac aspects of essential hypertension. *J Hypertens* 1984; 2: 121–125.
37. Weiss YA, Safar ME, London GM et al. Repeat hemodynamic determinations in borderline hypertension. *Am J Med* 1978; 64: 382–387.
38. Lund-Johansen P. Spontaneous changes in central haemodynamics in essential hypertension: A 10-year follow-up study. In: Onesti G, Klimt CR (eds). *Hypertension: Determinants, Complications and Intervention*. Grune & Stratton, New York; 1979:201–218.
39. Sannerstedt R. Hemodynamic response to exercise in patients with arterial hypertension. *Acta Med Scand* 1966; 458(Suppl 180): 1–83.
40. Amery A, Julius S, Whitlock LS. Influence of hypertension on the hemodynamic response to exercise. *Circulation* 1967; 36: 231–237.
41. Amery A. Hemodynamic changes during exercise in hypertensive patients. *Mallattie Cardiovasc* 1969; 10: 227–245.
42. Fagard R, Amery A. Physical exercise in hypertension. In: Laragh J, Brenner BM (eds). *Hypertension: Pathophysiology, Diagnosis, and Management*. Raven Press, New York; 1995:2669–2682.
43. Omvik P, Lund-Johansen P. Combined captopril and hydrochlorothiazide therapy in severe hypertension: Long-term haemodynamic changes at rest and during exercise. *J Hypertens* 1984; 2: 73–80.
44. Fouad FM, Tarazi RC, Gallagher JM et al. Abnormal left ventricular relaxation in hypertensive patients. *Clin Sci* 1980; 59: 411S–411S.
45. Wikstrand J. Diastolic function of the hypertrophied left ventricle in primary hypertension. *Clin Physiol* 1986; 6: 115–127.
46. Devereux RB, Savage DD, Sachs I et al. Relations of hemodynamic load to left ventricular hypertrophy and performance in hypertension. *Am J Cardiol* 1983; 51: 171–176.
47. Rooke GA, Feigl EO. Work as a correlate of canine left ventricular oxygen consumption, and the problem of catecholamine oxygen wasting. *Circ Res* 1982; 50: 273–286.
48. Lund-Johansen P. Blood pressure and heart rate responses during physical stress in hypertension: Modifications by drug treatment. *Eur Heart J Suppl* 1999; 1(Suppl B): B10–B17.
49. Wilenius M, Tikkanen AJ, Tahvanainen AM et al. Central wave reflection is associated with peripheral arterial resistance in addition to arterial stiffness in subjects without antihypertensive medication. *BMC Cardiovasc Disord* 2016; 16: 131.
50. Buus NH, Carlsen RK, Khatir DS et al. Arterial stiffness and peripheral resistance in offspring of hypertensive parents: Influence of sex and other confounders. *J Hypertens* 2018; 36(4): 815–823.
51. Asayama K, Hozawa A, Taquri M et al. Blood pressure, heart rate, and double product in a pooled cohort: The Japanese arteriosclerosis longitudinal study. *J Hypertens* 2017; 35: 1808–1815.
52. Okin PM, Gerds E, Kjeldsen SE et al. Gender differences in regression of ECH left ventricular hypertrophy during antihypertensive therapy. *Hypertension* 2008; 32: 100–106.
53. Regnault V, Thomas F, Safar ME et al. Sex difference in cardiovascular risk: Role of pulse pressure amplification. *J Am Coll Cardiol* 2012; 59: 1771–1777.
54. EU Gen Med Cardiovascular Clinical Study Group, Regitz-Zagrosek V, Oertel-Prigione S, Prescott E et al. Gender in cardiovascular diseases: Impact on clinical manifestations, management, and outcomes. *Eur Heart J* 2016; 37: 24–34.
55. Mancusi C, Gerds E, DeSimone G et al. Higher pulse pressure/stroke volume index is associated with impaired outcome in hypertensive patients with left ventricular hypertrophy. The LIFE study. *Blood Pressure* 2017; 26: 150–155.
56. Man in't Veld A, van den Meiracker AH. Effects of antihypertensive drugs on cardiovascular haemodynamics. In: Laragh JH, Brenner BM (eds). *Hypertension: Pathophysiology, Diagnosis, and Management*. 2nd ed. Raven Press, New York; 1995:2753–2764.
57. Lund-Johansen P. Antihypertensive drugs: Hemodynamic effects. In: McInnes G (ed). *Clinical Pharmacology and Therapeutics of Hypertension. Handbook of Hypertension*. Vol 24. Elsevier, Amsterdam; 2008.
58. Lund-Johansen P. Hemodynamic changes at rest and during exercise in long-term prazosin therapy of essential hypertension. *Postgrad Med* 1975; Spec No: 45–52.
59. Lund-Johansen P, Omvik P, Haugland H. Acute and chronic haemodynamic effects of doxazosin in hypertension at rest and during exercise. *Br J Clin Pharmacol* 1986; 21(Suppl 1): 45S–54S.
60. Omvik P, Lund-Johansen P. Long-term haemodynamic effects of sustained-release trimazosin at rest and during exercise in essential hypertension. *Eur J Clin Pharmacol* 1991; 40: 131–134.
61. Lund-Johansen P. Haemodynamic long-term effects of a new beta-adrenoceptor blocking drug, atenolol (ICI 66082), in essential hypertension. *Br J Clin Pharmacol* 1976; 3: 445–451.
62. Lund-Johansen P, Ohm OJ. Haemodynamic long-term effects of metoprolol at rest and during exercise in essential hypertension. *Br J Clin Pharmacol* 1977; 4: 147–151.
63. Lund-Johansen P. Hemodynamic long-term effects of timolol at rest and during exercise in essential hypertension. *Acta Med Scand* 1976; 199: 263–267.
64. Lund-Johansen P. Hemodynamic changes at rest and during exercise in long-term beta-blocker therapy of essential hypertension. *Acta Med Scand* 1974; 195: 117–121.
65. Lund-Johansen P. Long-term hemodynamic effects of bunitrolol at rest and during exercise in essential hypertension. *J Cardiovasc Pharmacol* 1979; 1: 77–83.
66. Lund-Johansen P. Long-term hemodynamic effects of penbutolol at rest and during exercise in essential hypertension. *Eur J Clin Pharmacol* 1979; 16: 149–153.
67. Omvik P, Lund-Johansen P, Haugland H. Modest antihypertensive effect of epanolol, a beta 1-selective receptor blocker with beta 1 agonist activity: An acute and long-term hemodynamic study at rest and during exercise and double crossover comparison with atenolol on ambulatory blood pressure. *Cardiovasc Drugs Ther* 1993; 7: 125–132.
68. Lund-Johansen P. Central haemodynamic effects of beta blockers in hypertension. A comparison between atenolol, metoprolol, timolol, penbutolol, alprenolol, pindolol and bunitrolol. *Eur Heart J* 1983; 4(Suppl D): 1–12.
69. Lund-Johansen P. Hemodynamic effects of verapamil in essential hypertension at rest and during exercise. *Acta Med Scand Suppl* 1984; 681: 109–115.
70. Lund-Johansen P, Omvik P. Effect of long-term diltiazem treatment on central haemodynamics and exercise endurance in essential hypertension. *Eur Heart J* 1990; 11: 543–551.
71. Omvik P, Lund-Johansen P. Acute and long-term hemodynamic effects of tiapamil at rest and during exercise in essential hypertension. *Cardiovasc Drugs Ther* 1989; 3: 517–523.
72. Lund-Johansen P, Omvik P. Chronic hemodynamic effects of tiapamil and felodipine in essential hypertension at rest and during exercise. *J Cardiovasc Pharmacol* 1990; 15(Suppl 4): S42–S47.
73. Lund-Johansen P, Omvik P. Haemodynamic effects of nifedipine in essential hypertension at rest and during exercise. *J Hypertens* 1983; 1: 159–163.
74. Omvik P, Lund-Johansen P, Haugland H. Nisoldipine. Central haemodynamics at rest and during exercise in essential hypertension: Acute and chronic studies. *J Hypertens* 1988; 6: 95–103.
75. Lund-Johansen P, Omvik P, White W et al. Long-term haemodynamic effects of amlodipine at rest and during exercise in essential hypertension. *J Hypertens* 1990; 8: 1129–1136.
76. Lund-Johansen P. Hemodynamic changes in long-term diuretic therapy of essential hypertension. A comparative study of chlorthalidone, polythiazide and hydrochlorothiazide. *Acta Med Scand* 1970; 187: 509–518.
77. Lund-Johansen P. Hemodynamic and metabolic long-term effects of tienilic acid in essential hypertension. *Acta Med Scand Suppl* 1981; 646: 106–114.
78. Lund-Johansen P, Omvik P. Long-term haemodynamic effects of enalapril (alone and in combination with hydrochlorothiazide) at rest and during exercise in essential hypertension. *J Hypertens Suppl* 1984; 2: S49–S56.
79. Omvik P, Lund-Johansen P. Comparison of long-term hemodynamic effects at rest and during exercise of lisinopril plus sodium restriction versus hydrochlorothiazide in essential hypertension. *Am J Cardiol* 1990; 65: 331–338.
80. Omvik P, Lund-Johansen P. Acute haemodynamic effects of perindoprilat in essential hypertension at rest and during exercise. *J Hypertens* 1989; 7: 633–638.
81. Lund-Johansen P, Bakke OM. Haemodynamic effects and plasma concentrations of labetalol during long-term treatment of essential hypertension. *Br J Clin Pharmacol* 1979; 7: 169–174.
82. Lund-Johansen P, Omvik P. Chronic haemodynamic effects of carvedilol in essential hypertension at rest and during exercise. *Eur Heart J* 1992; 13: 281–286.

83. Lund-Johansen P, Omvik P. Acute and chronic hemodynamic effects of drugs with different actions on adrenergic receptors: A comparison between alpha blockers and different types of beta blockers with and without vasodilating effect. *Cardiovasc Drugs Ther* 1991; 5: 605–615.
84. Lund-Johansen P, Omvik P. Prizidilol in essential hypertension: Long-term effects on plasma volume, extracellular fluid volume, and central hemodynamics at rest and during exercise. *J Cardiovasc Pharmacol* 1982; 4: 1012–1017.
85. Omvik P, Lund-Johansen P. Is sodium restriction effective treatment of borderline and mild essential hypertension? A long-term haemodynamic study at rest and during exercise. *J Hypertens* 1986; 4: 535–541.
86. Omvik P, Myking OL. Unchanged central hemodynamics after six months of moderate sodium restriction with or without potassium supplement in essential hypertension. *Blood Press* 1995; 4: 32–41.
87. Lund-Johansen P. Hemodynamic changes in long-term -methyldopa therapy of essential hypertension. *Acta Med Scand* 1972; 192: 221–226.
88. Lund-Johansen P. Hemodynamic changes at rest and during exercise in long-term clonidine therapy of essential hypertension. *Acta Med Scand* 1974; 195: 111–115.
89. Omvik P, Lund-Johansen P. Long-term effects on central haemodynamics and body fluid volumes of ketanserin in essential hypertension studies at rest and during dynamic exercise. *J Hypertens* 1983; 1: 405–412.
90. Omvik P, Gerds E, Myking OL, Lund-Johansen P. Long-term central hemodynamic effects at rest and during exercise of losartan in essential hypertension. *Am Heart J* 2000; 140: 624–630.
91. Omvik P, Lund-Johansen P. Comparison of the hemodynamic effects of five calcium channel blockers at rest and during exercise in essential hypertension. *Ann Clin Res* 1988; 20(Suppl 48): 23–30.
92. Fuchs S, Philippe J, Corvol P, Pinet F. Implications of Ref-1 in the repression of renin gene transcription by intracellular calcium. *J Hypertension* 2003; 21: 327–335.
93. Kiowski W, Lüscher TF, Linder L, Bühler FR. Endothelin-1-induced vasoconstriction in humans. Reversal by calcium channel blockade but not by nitrovasodilators or endothelium-derived relaxing factor. *Circulation* 1991; 83: 469–475.
94. Kiowski W, Linder L. Reversal of endothelin-1-induced vasoconstriction by nifedipine in human resistance vessels *in vivo* in healthy subjects. *Am J Cardiol* 1992; 69: 1063–1066.
95. Kiowski W, Erne P, Bertel O et al. Acute and chronic sympathetic reflex activation and antihypertensive response to nifedipine. *JACC* 1986; 7: 344–348.
96. Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; 34: 2159–2219.
97. James PA, Oparil S, Carter BL et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults. Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311: 507–520.
98. Omvik P, Enger E, Eide I. Effect of sodium depletion on plasma renin concentration before and during adrenergic beta-receptor blockade with propranolol in normotensive man. *Am J Med* 1976; 6: 608–614.
99. Tarazi RC, Dustan HP, Frohlich E. Long-term thiazide therapy in essential hypertension. Evidence for persistent alteration in plasma volume and renin activity. *Circulation* 1970; 41(4): 709–717.
100. Malik RA, Schofield IJ, Izzard A et al. Effects of angiotensin type-1 receptor antagonism on small artery function in patients with type 2 diabetes mellitus. *Hypertension* 2005; 45: 264–269.
101. Lauwers P, Conway J. Effect of long-term treatment with chlorthiazide on body fluids, serum electrolytes and exchangeable sodium in hypertensive patients. *J Lab Clin Med* 1960; 56: 401–408.
102. Pucci G, Ranalli MG, Battista F, Schillaci G. Pressure: Systematic review and meta-analysis of randomized trials in hypertension effects of b-blockers with and without vasodilating properties on central blood. *Hypertension* 2016; 67: 316–324.
103. Lund-Johansen P. Pharmacology of combined alpha-beta-blockade. II. Haemodynamic effects of labetalol. *Drugs* 1984; 28(Suppl 2): 35–50.
104. van Zwieten PA. Pharmacology of centrally acting hypotensive drugs. *Br J Clin Pharmacol* 1980; 10(Suppl 1): 13S–20S.
105. Laragh JH. Vasoconstriction-volume analysis for understanding and treating hypertension: The use of renin and aldosterone profiles. *Am J Med* 1973; 55: 261–274.
106. Graudal NA, Hubeck-Graudal T, Jürgens G. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. *Cochrane Database Syst Rev* 2017; 4: CD004022.
107. Omvik P, Gerds E, Myking O, Lund-Johansen P. Similar central hemodynamics in salt-sensitive and salt-resistant hypertensive patients. *Blood Press* 1999; 8: 233–241.
108. Gerds E, Lund-Johansen P, Omvik P. Reproducibility of salt sensitivity testing using a dietary approach in essential hypertension. *J Hum Hypertens* 1999; 13: 375–384.
109. Mente A, O'Donnell M, Rangarajan S et al. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: A pooled analysis of data from four studies. *Lancet* 2016; 388: 465–475.
110. Lund-Johansen P. Hemodynamic consequences of long-term beta-blocker therapy: A 5-year follow-up study of atenolol. *J Cardiovasc Pharmacol* 1979; 1: 487–495.
111. Mulvany MJ. Effects of angiotensin-converting enzyme inhibition on vascular remodelling of resistance vessels in hypertensive patients. *Metabolism* 1998; 47(Suppl 1): 20–23.
112. Christensen L, Mulvany MJ. Vasodilatation, not hypotension, improves resistance vessel design during treatment of essential hypertension: A literature survey. *J Hypertension* 2001; 19: 1001–1008.
113. Palatini P, Casiglia E, Gasowski J et al. Arterial stiffness, central hemodynamics, and cardiovascular risk in hypertension. *Vasc Health Risk Manag* 2011; 7: 725–739.
114. Williams B, Lacy PS, Thom SM et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: Principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006; 113: 1213–1225.
115. Wachtell K, Palmieri V, Olsen MH et al. Change in systolic left ventricular performance after 3 years of antihypertensive treatment: The Losartan Intervention for Endpoint (LIFE) Study. *Circulation* 2002; 106: 227–232.



# GENETIC BASIS OF BLOOD PRESSURE AND HYPERTENSION

# 7

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## INTRODUCTION

The high prevalence of hypertension (HTN) and its consequent significant adverse economic impact on the individual and population highlights the importance of understanding its causation and developing effective early primary prevention measures to interrupt and prevent the continuing and expensive cycle of managing HTN and its complications (1).

During most of the twentieth century, the 'germ theory' model dominated etiological explanations of disease. The prevalent model now is a 'gene model', where for many common diseases genetic studies are beginning to revise the current taxonomy of disease through identification of genetic variants that define disease subtypes. The concept of genetic disease has not remained stable but has changed from the fairly restricted notion of a disease traceable to a single gene defect with 100% heritability to the present extended usage where it includes common diseases and even complex behavioural traits such as alcoholism. HTN, asthma and coronary heart diseases are all defined as complex multifactorial diseases, which are the result of long-term, often subtle, gene–environment interactions. This means that for predicting and understanding these diseases, individual life histories may be as important as population histories.

## EVOLUTIONARY ASPECTS OF BLOOD PRESSURE AND HYPERTENSION

From an evolutionary perspective, essential HTN is a disease of civilization with its abundance of processed foods and long lifespan. The lifestyle characteristics of modern societies are ideal risk factors for the development of HTN. This risk may be augmented by genotypes that have optimised fitness in the salt poor ancient environment, but have become maladaptive in the modern context (2–5). The evolutionary transition of animal life from the salt-rich oceans to salt-poor land has resulted in development of regulatory mechanisms to conserve salt in the body. When early humans adopted modern behaviour, emerging >50,000 years ago, they lived in this primarily salt-poor

environment consuming <690 mg of salt per day. With the development of agriculture 10,000 years ago, salt intake became even lower, as plants made up 90% of the diet. For this reason, ancestral humans developed a mainly kidney-based regulatory mechanism for the conservation of extracellular fluid concentrations, and natural selection over generations moulded their adaptation to the low salt content in their environment. However, in modern society access to salt is almost unlimited, with a sodium consumption of about 4 g or more per/day (equivalent to 10 g salt) (2). In the last 10,000 years, the change in human DNA was at most 0.005%, but human physiology and biochemistry now face circumstances vastly different from those that were selected by evolution. This difference between the human organism and its life environment may account for the current high prevalence of chronic diseases such as HTN, obesity and atherosclerosis, amplified by the undesirable pleiotropic effects of genotypes that were beneficial for early humans. This echoes the 'thrifty gene' hypothesis (3) proposed by James Neel to explain the tendency towards obesity and diabetes. This hypothesis postulates that certain genes in humans have evolved to maximize metabolic efficiency, lipid storage, and food searching behaviour that was advantageous during the hunter-gatherer period of human history, and for puberty or child-bearing women during periods of famine. Now in times of abundance of high fat, high carbohydrate, low fibre diets and relative inactivity, this genotype has led to the epidemic of obesity and diabetes. Differing predispositions to a trait in different populations may reflect different evolutionary selection pressures and the fact that populations do not share the same ancestral histories. It is recognized that HTN occurs earlier and with more severity in people of African ancestry compared to those of European ancestry (although clearly non-genetic factors may contribute) (6,7). The rates of HTN and sodium sensitivity are generally higher in individuals carrying the ancestral alleles of sodium-conserving genes, which show strong latitudinal clines with the ancestral sodium-conserving alleles more prevalent in African populations and less so in the northern regions (8–10). In addition, the high prevalence of chronic diseases in the newly emerging economies may reflect the effect of the 'thrifty phenotype'. In poor nutritional conditions, a pregnant female can modify the development of her unborn child

such that it will be prepared for survival in an environment in which resources are likely to be short, resulting in a thrifty phenotype. The mismatch between early- and late-life nutritional status renders those born in poverty and growing into plenty especially vulnerable (7). It is also hypothesized that the renin-angiotensin-aldosterone system (RAAS) was initially adapted for sodium conservation and may be maladaptive in modern societies with ready access to dietary sodium (11).

## HERITABILITY OF BLOOD PRESSURE AND HYPERTENSION

Family studies have consistently demonstrated a genetic component influencing blood pressure (BP) and HTN. The Montreal Adoption Study (12) demonstrated correlation coefficients of 0.38 and 0.16 between biological and adoptive sibs respectively, while the Victorian Family Heart Study (13) estimated correlation coefficients of 0.44 for non-twin siblings, 0.78 for monozygous twins, 0.50 for dizygous twins and 0.12 for spouse-spouse pairs. All these data indicate presence of a genetic component if the environmental influence is assumed to be similar between comparison groups. Hunt et al. (14) showed familial aggregation of HTN from an analysis of life table data for 94,292 persons and found the relative risks of developing HTN were 4.1 in men and 5 in women aged 20–39 who had at least two first-degree relatives affected by HTN. Two additional measures commonly used to assess the genetic component of a trait are:

- **Heritability ( $h^2$ ):** The fraction of variation in disease susceptibility due to genetic factors.
- **Sibling recurrent risk ( $\lambda_s$ ):** The degree of elevated risk of disease for a sibling of an affected individual compared with a member of the general population.

The heritability of clinic systolic BP and diastolic BP is around 15–40% and 15–30% respectively, whereas for ambulatory nighttime systolic and diastolic BP the heritabilities are 32–70% and 32–50% (15–21). It is pertinent to point out that though the heritability estimates are considerable, this does not equate to magnitude of genetic effect. This is because the denominator in the estimate of heritability comprises measurement error and variances attributable to genes, shared environment, non-shared environment and unmeasured determinants. Heritability is also a property of the population studied, and low heritability estimates would suggest that genetic mapping would be difficult for that phenotype. The sibling recurrent risk ( $\lambda_s$ ) of HTN is around 1.2–1.5 (22), and taking this along with heritability and correlation estimates, HTN and BP can be considered a trait with relatively modest genetic effect ( $\lambda_s$  – CAD = 2.0–3.9; type 2 diabetes = 4.3; type 1 diabetes = 15; Huntington disease = 2000).

## COMMON VARIANT OR RARE VARIANT

Single-nucleotide polymorphisms (SNPs) defined based on a minor allele frequency (MAF) >1% are known as common variants. These account for more than 90% of the genetic differences between individuals and have no effect

on reproductive fitness. Two contrasting models have been proposed to explain the genetic basis for common diseases:

- **The common disease/common variant hypothesis:** It holds that complex traits are caused by common genetic variants which have undergone little or no selection in earlier populations and are likely to date back >100,000 years (23,24). The individual effects of these variants on the disease phenotype are small, and numerous variants in multiple genes are needed to express the trait. Moreover, as the human population rapidly expanded from a small founder pool over a short period, there was not enough time for new alleles generated during population growth to dilute out the disease-risk alleles that were common in the founder population (24,25).
- **The common disease rare variant hypothesis:** It posits an inverse relationship between the magnitude of genetic effect and allele frequency. This indicates that the high frequency of common diseases is not due to the cumulative effect of numerous common variants but to rare variants on a background of highly prevalent environmental influences. There is evidence that the recent explosive human population growth has resulted in an excess of rare genetic variants, with almost 86% of the deleterious mutations arising in the past 5000–10,000 years (26). This would indicate that rare variants have a role in determining common phenotypes supported by data showing rare nonsynonymous variants in salt-handling genes have comparatively larger effects on BP in the general population (27).

This is reminiscent of the Platt-Pickering debate in the 1950s (5,28), when Platt argued that HTN was a dichotomous trait and a simple Mendelian disease while Pickering thought BP was inherited as a 'graded character', and hence a complex non-Mendelian trait (28,29). The normal unimodal distribution of BP in the general population supports the complex multifactorial basis of BP regulation (30–32). This is further put forth by the discovery of numerous SNPs from genome-wide association studies (GWAS) associated with BP and HTN (33–38). Platt's hypothesis would require a bimodal distribution of BP in the general population which is not evident, but Platt's view is not entirely discounted as there exist highly penetrant rare genetic variants with large effects in families with Mendelian forms of HTN and hypotension (39).

## BLOOD PRESSURE REGULATORY PATHWAYS AND THEIR GENETIC BASIS

The identification of rare mutations in genes causing monogenic forms of HTN come from linkage analysis of pedigrees exhibiting a Mendelian pattern of inheritance of the BP phenotype. In contrast, the standard method for genetic dissection of a complex trait is a GWAS which is based on the common disease/common variant hypothesis. GWAS analyses have identified nearly 200 SNPs associated with BP and continue to discover more associations with studies of increasing sample sizes (top GWAS signals are summarised in Table 7.1). However, the percentage of the BP trait variance explained by all the SNPs is less than 5% (40–44).

| Table 7.1 Summary of genome-wide association study results for blood pressure and hypertension |            |          |              |                   |       |         |           |       |                              |
|------------------------------------------------------------------------------------------------|------------|----------|--------------|-------------------|-------|---------|-----------|-------|------------------------------|
| Locus                                                                                          | SNP        | Genotype | Coded allele | Coded allele freq |       |         | BP effect |       |                              |
|                                                                                                |            |          |              | European          | Asian | African | European  | Asian | African                      |
| 1p36.2                                                                                         | rs880315   | C/T      | C            | 0.35              | 0.59  | 0.16    | ↑         | ↑     | CASZ1                        |
| 1p36.22                                                                                        | rs17367504 | A/G      | G            | 0.17              | 0.10  | 0.06    | ↓         | ↓     | MTHFR, CLCN6, NPPA, NPPB     |
|                                                                                                | rs5068     | C/T      | C            | 0.07              | 0.00  | 0.01    | ↓         |       |                              |
| 1p13.2                                                                                         | rs2932538  | C/T      | C            | 0.73              | 0.80  | 0.85    | ↓         |       | SLC16A1, CAPZA1, ST7L, MOV10 |
|                                                                                                | rs17030613 | A/C      | C            | 0.19              | 0.45  | 0.05    |           | ↑     |                              |
|                                                                                                | rs10745332 | A/G      | A            | 0.74              | 0.81  | 0.77    |           | ↑     |                              |
|                                                                                                | rs2169137  | C/G      | G            | 0.74              | 0.94  | 0.80    | ↑         |       | MDM4                         |
| 1q42.2                                                                                         | rs2004776  | A/G      | A            | 0.26              | 0.67  | 0.54    | ↑         |       | AGT                          |
| 2p23.2                                                                                         | rs1275988  | A/G      | A            | 0.60              | 0.23  | 0.08    | ↓         |       | KCNK3                        |
| 2q11.2                                                                                         | rs7599598  | A/G      | A            | 0.57              | 0.63  | 0.09    | ↓         |       | FER1L5                       |
| 2q24.3                                                                                         | rs1446468  | A/G      | A            | 0.53              | 0.47  | 0.96    | ↓         |       | FIGN                         |
|                                                                                                | rs13002573 | A/G      | G            | 0.25              | 0.40  | 0.11    | ↓         |       | FIGN                         |
|                                                                                                | rs16849225 | C/T      | C            | 0.75              | 0.59  | 0.94    |           | ↑     | FIGN                         |
|                                                                                                | rs6749447  | G/T      | G            | 0.28              | 0.72  | 0.58    | ↑         |       | STK39                        |
| 2q32.1                                                                                         | rs16823124 | A/G      | A            | 0.23              | 0.51  | 0.10    | ↑         |       | PDE1A                        |
| 3p25.3                                                                                         | rs347591   | G/T      | G            | 0.33              | 0.23  | 0.51    | ↓         |       | HRH1-ATG7                    |
| 3p24.1                                                                                         | rs13082711 | C/T      | T            | 0.80              | 0.94  | 0.96    | ↓         |       | SLC4A                        |
|                                                                                                | rs820430   | C/T      | T            | 0.64              | 0.40  | 1.00    | ↑         |       |                              |
| 3p22.1                                                                                         | rs9815354  | A/G/T    | A            | 0.23              | 0.12  | 0.17    | ↑         | ↑     | ULK4                         |
|                                                                                                | rs3774372  | C/T      | T            | 0.77              | 0.87  | 0.81    | ↓         |       |                              |
|                                                                                                | rs1717027  | C/T      | T            | 0.22              | 0.12  | 0.66    | ↑         |       |                              |
| 3p21.31                                                                                        | rs319690   | A/G      | A            | 0.51              | 0.75  | 0.41    | ↑         |       | MAP4                         |
|                                                                                                | rs7651237  | A/G      | G            | 0.64              | 0.94  | 0.88    | ↑         |       |                              |

(Continued)

| Locus   | SNP        | Genotype | Coded allele | Coded allele freq |       |         | BP effect               |       |         | Nearest gene(s) |
|---------|------------|----------|--------------|-------------------|-------|---------|-------------------------|-------|---------|-----------------|
|         |            |          |              | European          | Asian | African | European                | Asian | African |                 |
| 3p21.1  | rs9810888  | G/T      | G            | 0.53              | 0.59  | 0.46    |                         | ↑     |         | CACNA1D         |
| 3q26.1  | rs16833934 | A/G      | G            | 0.37              | 0.17  | 0.65    | ↓                       |       |         | MIR1263         |
| 3q26.2  | rs419076   | G/T      | T            | 0.48              | 0.13  | 0.57    | ↑                       |       |         | MECOM           |
| 4q12    | rs871606   | A/G      | A            | 0.87              | 0.78  | 0.76    | ↑                       | ↑     |         | CHIC2           |
| 4q21.21 | rs16998073 | A/T      | T            | 0.19              | 0.30  | 0.05    | ↑                       | ↑     |         | FGF5            |
|         | rs1458038  | A/G      | A            | 0.27              | 0.34  | 0.05    | ↑                       |       |         |                 |
| 4q24    | rs13107325 | A/C/T    | T            | 0.10              | 0.00  | 0.00    | ↓                       |       |         | SLC39A8         |
| 4q25    | rs6825911  | C/T      | C            | 0.20              | 0.48  | 0.54    |                         | ↑     |         | ENPEP, PITX2    |
| 4q32.1  | rs13139571 | A/C      | C            | 0.74              | 0.68  | 0.88    | ↑                       |       |         | GUCY1A3-GUCY1B3 |
| 5p13.3  | rs1173771  | C/T      | C            | 0.51              | 0.57  | 0.81    | ↑                       |       |         | NPR3-C5orf23    |
|         | rs7733331  | C/T      | T            | 0.50              | 0.42  | 0.42    | ↓                       |       |         |                 |
|         | rs1173766  | C/T      | C            | 0.52              | 0.59  | 0.62    |                         | ↑     |         |                 |
| 5q33.3  | rs11953630 | A/C/T    | T            | 0.34              | 0.06  | 0.15    | ↓                       |       |         | EBF1            |
| 6p22.2  | rs1799945  | C/G      | G            | 0.18              | 0.04  | 0.00    | ↑                       | ↑     |         | HFE             |
|         | rs198823   | G/T      | T            | 0.65              | 0.23  | 0.60    | ↓                       |       |         |                 |
| 6p21.33 | rs805303   | C/T      | C            | 0.70              | 0.57  | 0.30    | ↑                       |       |         | BAG1            |
|         | rs2021783  | C/T      | C            | 1.00              | 0.81  | 1.00    |                         | ↑     |         | CYP21A2         |
| 6p21.32 | rs2854275  | G/T      | T            | 0.08              | 0.03  | 0.08    | ↓                       |       |         | H1A-DQB1        |
| 6p21.1  | rs10948071 | C/T      | T            | 0.70              | 0.67  | 0.05    | ↓                       |       |         | CRIP3           |
| 6p24.1  | rs9349379  | A/G      | A            | 0.59              | 0.96  | 0.25    | Fibromuscular dysplasia |       |         | PHACTR1         |
| 6q22.33 | rs13209747 | C/G/T    | T            | 0.45              | 0.48  | 0.12    |                         | ↑     | ↑       | RSPO3           |
| 6q25.1  | rs17080102 | C/G      | C            | 0.06              | 0.01  | 0.09    | ↓                       | ↓     | ↓       | PLEKHG1         |
| 7p15.2  | rs17428471 | G/T      | T            | 0.08              | 0.05  | 0.14    | ↑                       | ↑     | ↑       | EVX1-HOXA       |

(Continued)

| Table 7.1 (Continued) Summary of genome-wide association study results for blood pressure and hypertension |            |          |              |                   |       |         |           |       |         |                 |
|------------------------------------------------------------------------------------------------------------|------------|----------|--------------|-------------------|-------|---------|-----------|-------|---------|-----------------|
| Locus                                                                                                      | SNP        | Genotype | Coded allele | Coded allele freq |       |         | BP effect |       |         | Nearest gene(s) |
|                                                                                                            |            |          |              | European          | Asian | African | European  | Asian | African |                 |
| 7p12.3                                                                                                     | rs2949837  | A/T      | A            | 0.23              | 0.61  | 0.00    | ↑         |       |         | IGFBP3          |
| 7q21.2                                                                                                     | rs2282978  | C/T      | C            | 0.36              | 0.06  | 0.43    | ↑         |       |         | CDK6            |
| 7q22.3                                                                                                     | rs17477177 | C/T      | T            | 0.72              | 0.91  | 0.93    | ↓         |       |         | PIK3CG          |
|                                                                                                            | rs12705390 | A/G      | G            | 0.72              | 0.91  | 0.93    | ↓         |       |         |                 |
| 7q36.1                                                                                                     | rs3918226  | C/T      | T            | 0.10              | 0.00  | 0.00    | ↑         |       |         | NOS3            |
| 8p23.1                                                                                                     | rs4841569  | A/G      | G            | 0.57              | 1.00  | 0.89    | ↑         |       |         | BLK-GATA4       |
|                                                                                                            | rs2898290  | C/T      | C            | 0.58              | 0.02  | 0.55    | NR        |       |         |                 |
| 8q24.12                                                                                                    | rs2071518  | C/T      | T            | 0.20              | 0.19  | 0.60    | ↑         |       |         | NOV             |
| 10p12.31                                                                                                   | rs11014166 | A/T      | A            | 0.63              | 0.97  | 0.89    | ↑         | ↓     |         | CACNB2          |
|                                                                                                            | rs1813353  | A/G      | A            | 0.65              | 0.92  | 0.85    | ↑         |       |         |                 |
|                                                                                                            | rs4373814  | C/G      | G            | 0.63              | 0.53  | 0.43    | ↓         |       |         |                 |
|                                                                                                            | rs12258967 | C/G      | C            | 0.64              | 1.00  | 0.73    | ↑         |       |         |                 |
| 10q21.2                                                                                                    | rs1530440  | C/T      | T            | 0.16              | 0.20  | 0.02    | ↓         |       |         | c10orf107       |
|                                                                                                            | rs4590817  | C/G      | G            | 0.82              | 1.00  | 0.82    | ↑         |       |         |                 |
|                                                                                                            | rs12244842 | G/T      | T            | 0.25              | 0.19  | 0.35    | ↓         |       |         |                 |
|                                                                                                            | rs7070797  | A/G      | A            | 0.15              | 0.00  | 0.00    | ↓         |       |         |                 |
| 10q22.2                                                                                                    | rs4746172  | C/T      | C            | 0.23              | 0.56  | 0.19    | ↑         |       |         | VCL             |
| 10q23.33                                                                                                   | rs932764   | A/G      | G            | 0.43              | 0.58  | 0.15    | ↑         |       |         | PLCE1           |
| 10q24.32                                                                                                   | rs1004467  | C/T      | T            | 0.92              | 0.67  | 0.81    | ↑         |       |         | CYP17A1-NT5C2   |
|                                                                                                            | rs11191548 | C/T      | T            | 0.92              | 0.72  | 0.99    | ↑         | ↑     |         |                 |
|                                                                                                            | rs12413409 | A/G      | G            | 0.92              | 0.72  | 0.98    |           | ↑     |         |                 |
|                                                                                                            | rs4409766  | C/T      | T            | 0.93              | 0.78  | 0.82    |           | ↑     |         |                 |
|                                                                                                            | rs3824755  | C/G      | C            | 0.07              | 0.23  | 0.17    | ↓         |       |         |                 |

(Continued)

**Table 7.1 (Continued)** Summary of genome-wide association study results for blood pressure and hypertension

| Locus    | SNP        | Genotype | Coded allele | Coded allele freq |       |         | BP effect |       |         | Nearest gene(s)         |
|----------|------------|----------|--------------|-------------------|-------|---------|-----------|-------|---------|-------------------------|
|          |            |          |              | European          | Asian | African | European  | Asian | African |                         |
| 10q25.3  | rs2782980  | C/T      | T            | 0.27              | 0.15  | 0.44    | ↓         |       |         | ADRB1                   |
|          | rs7076938  | C/T      | C            | 0.33              | 0.17  | 0.45    | ↓         |       |         |                         |
|          | rs1801253  | C/G      | G            | 0.32              | 0.15  | 0.41    | ↓         |       |         |                         |
| 11p15.5  | rs661348   | C/T      | C            | 0.45              | 0.58  | 0.11    | ↑         |       |         | LSP1-TNNT3              |
| 11p15.4  | rs7129220  | A/G      | G            | 0.89              | 1.00  | 0.95    | ↓         |       |         | ADM                     |
| 11p15.1  | rs381815   | A/C/T    | T            | 0.30              | 0.25  | 0.18    | ↑         |       |         | PLEKHA7                 |
|          | rs757081   | C/G      | G            | 0.63              | 0.66  | 1.00    | ↑         |       |         | PIK3C2A, NUCB2, NCR3LG1 |
| 11p15.2  | rs2014408  | C/T      | T            | 0.20              | 0.21  | 0.03    | ↑         | ↑     | ↑       | SOX6                    |
|          | rs4757391  | C/T      | C            | 0.18              | 0.17  | 0.23    |           | ↑     |         |                         |
| 11q13.1  | rs4601790  | A/G      | G            | 0.25              | 0.42  | 0.07    | ↑         |       |         | EHBP1L1                 |
|          | rs3741378  | A/G      | A            | 0.15              | 0.38  | 0.36    | ↓         |       |         | RELA                    |
| 11q22.1  | rs633185   | C/G      | G            | 0.68              | 0.55  | 0.82    | ↓         |       |         | FLJ32810-TMEM133        |
| 11q24.3  | rs11222084 | A/T      | T            | 0.40              | 0.07  | 0.26    | ↑         |       |         | ADAMTS8                 |
| 12q13.13 | rs7297416  | A/C      | C            | 0.25              | 0.62  | 0.38    | ↓         |       |         | HOXC4                   |
| 12q21.33 | rs11105354 | A/G      | G            | 0.12              | 0.42  | 0.11    | ↓         |       |         | ATP2B1                  |
|          | rs2681492  | A/G      | A            | 0.88              | 0.58  | 0.84    | ↑         |       |         |                         |
|          | rs2681472  | C/T      | T            | 0.88              | 0.58  | 0.89    | ↑         | ↑     |         |                         |
|          | rs17249754 | A/G      | G            | 0.88              | 0.59  | 0.84    | ↑         | ↑     |         |                         |
| 12q24.12 | rs3184504  | C/T      | T            | 0.45              | 0.00  | 0.00    | ↑         |       |         | SH2B3                   |
| 12q24.13 | rs653178   | A/G      | A            | 0.56              | 1.00  | 1.00    | ↓         |       |         |                         |
|          | rs11066280 | A/T      | T            | 1.00              | 0.75  | 1.00    |           | ↑     |         | RPL6-ALDH2              |

(Continued)



**Table 7.1 (Continued)** Summary of genome-wide association study results for blood pressure and hypertension

| Locus    | SNP        | Genotype | Coded allele | Coded allele freq |       |         | BP effect |       |         | Nearest gene(s) |
|----------|------------|----------|--------------|-------------------|-------|---------|-----------|-------|---------|-----------------|
|          |            |          |              | European          | Asian | African | European  | Asian | African |                 |
| 12q24.21 | rs35444    | C/T      | T            | 0.59              | 0.73  | 0.55    | ↑         |       |         | TBX5-TBX3       |
|          | rs2384550  | A/G      | A            | 0.37              | 0.09  | 0.34    | ↓         |       |         |                 |
|          | rs10850411 | C/T      | T            | 0.72              | 0.46  | 0.66    | ↑         |       |         |                 |
|          | rs1991391  | C/T      | C            | 0.64              | 0.91  | 0.58    | ↑         |       |         |                 |
|          | rs11067763 | A/G      | A            | 0.89              | 0.61  | 0.65    |           | ↑     |         | MED13L          |
| 15q21.1  | rs1036477  | A/G      | G            | 0.10              | 0.42  | 0.61    | ↓         |       |         | FBN1            |
| 15q24.1  | rs6495122  | A/C      | A            | 0.38              | 0.78  | 0.78    | ↑         |       |         | CYP11A1-JLK3    |
|          | rs1378942  | G/T      | G            | 0.32              | 0.79  | 1.00    | ↑         |       |         |                 |
| 15q24.2  | rs11072518 | C/T      | T            | 0.34              | 0.42  | 0.44    | ↑         |       |         | COX5A           |
|          | rs1133323  | A/G      | A            | 0.59              | 0.17  | 0.00    | ↓         |       |         |                 |
| 15q26.1  | rs2521501  | A/T      | T            | 0.63              | 0.93  | 0.80    | ↑         |       |         | FURIN-FES       |
| 16p12.3  | rs13333226 | A/G      | G            | 0.18              | 0.05  | 0.38    | ↑         |       |         | UMOD            |
|          | rs33063    | A/G      | A            | 0.19              | 0.15  | 0.00    | ↑         |       |         | NFAT5           |
| 17q21.31 | rs12946454 | C/T      | T            | 0.71              | 0.62  | 0.80    | ↑         |       |         | PLCD3           |
| 17q21.32 | rs17608766 | C/T      | T            | 0.91              | 1.00  | 1.00    | ↓         |       |         | GOSR2           |
| 17q21.33 | rs12940887 | C/T      | T            | 0.41              | 0.09  | 0.03    | ↑         |       |         | ZNF652          |
|          | rs16948048 | A/G      | G            | 0.42              | 0.09  | 0.42    | ↑         |       |         |                 |
| 20p12.2  | rs1327235  | A/G      | G            | 0.52              | 0.48  | 0.53    | ↑         |       |         | JAG1            |
|          | rs1887320  | A/G      | A            | 0.58              | 0.43  | 0.54    |           | ↑     |         |                 |
| 20q13.32 | rs6015450  | A/G      | G            | 0.07              | 0.00  | 0.22    | ↑         |       |         | GNAS-EDN3       |
|          | rs6092743  | A/G      | A            | 0.06              | 0.00  | 0.06    | ↑         |       |         | C20orf174       |

Source: Padmanabhan S, Joe, B. *Physiol Rev* 2017; 97(4): 1469–1528.

## SODIUM AND INTRAVASCULAR VOLUME

Vascular volume is a primary determinant of arterial pressure over the long term, and sodium acts as the principal determinant of extracellular fluid volume. Epidemiologic studies have linked dietary NaCl intake with HTN (45,46), with non-chloride salts of sodium having little or no effect on BP (47,48). Sodium homeostasis is maintained primarily by the kidneys. The renal glomeruli of a 70-kg man filter ~25,000 mEq of Na<sup>+</sup> and 180 L of water per day, and 99–100% of this amount is reabsorbed in different segments of the nephron – proximal convoluted tubule (60%), the thick ascending limb of the Henle loop (30%), the distal convoluted tubule (7%) and the connecting and the collecting duct (0–3%, controlled by aldosterone and angiotensin-2) (49), pointing to the critical role of the kidneys in sodium balance.

There are multiple lines of evidence supporting the link between the kidney, sodium and HTN. Guyton's 'pressure-natriuresis' model posits that arterial pressure increases in response to a high NaCl intake, in turn leading to increases in urinary sodium excretion to maintain sodium balance (30–32). Renal transplant studies in rats and in humans have shown that the HTN status of the donor has a major impact on long-term BP in the recipients (50,51). Finally, Mendelian forms of syndromic hypotension and HTN (39) have all been linked to mutations in genes whose encoded proteins regulate salt–water balance in the kidney, supporting the primacy of the kidneys in BP regulation. The RAAS contributes to the regulation of BP not only through the salt-retaining properties of the mineralocorticoid hormone aldosterone (*CYP11B2*) but also through the vasoconstrictor properties of angiotensin II. RAAS involves the renin (*REN*) acting on angiotensinogen (*AGT*), to form an inactive decapeptide, angiotensin I, which is converted by an angiotensin-converting enzyme (*ACE*) to angiotensin II which binds to angiotensin II receptors (*AGTR1*). *ACE* also cleaves and inactivates a number of other peptides including the vasodilator bradykinin, which is cleaved from kininogen (*KNG1*) by kallikrein (*KLK1*) (Figure 7.1).

## NA<sup>+</sup> HOMEOSTASIS

Na<sup>+</sup> reabsorption is controlled by mineralocorticoid active steroid hormones in both the distal convoluted tubule and the collecting duct (Figure 7.1). The amiloride-sensitive epithelial Na<sup>+</sup> channel (ENaC; *SCNN1A*, *SCNN1B*, *SCNN1G*, *SCNN1D*) is found predominantly in principal cells of the collecting duct and the thiazide-sensitive sodium chloride cotransporter (NCC; *SLC12A3*) in the distal convoluted tubule. In addition, basolateral sodium-potassium adenosine triphosphate (*ATP1A1-3*, *ATP1B1-4*) and the luminal renal outer medulla K<sup>+</sup> channel (ROMK; *KCNJ1*) are responsible for Na<sup>+</sup> and K<sup>+</sup> homeostasis. Aldosterone binds to the cytosolic mineralocorticoid receptor (MR; *NR3C2*) and leads to increased activity of the apical Na<sup>+</sup> transporter, ENaC. Deoxycorticosterone and deoxycortisol and their metabolites are alternative agonists of the MR, with cortisol being the most important one. The 11β-hydroxysteroid dehydrogenase type 2 enzyme (*HSD11B2*), which converts active cortisol to the inactive cortisone, protects the MR from cortisol, an alternative agonist of the MR, thus establishing the aldosterone specificity of the MR. Additional regulatory elements that

are involved include, but are not limited to, WNK (with no lysine) kinases – a family of large serine/threonine protein kinases (*WNK1* and *WNK4*) (52). While *WNK1* is widely expressed, *WNK4* is expressed primarily in the kidney, localized to tight junctions. *WNK4* is responsible for tonic inhibition of the thiazide-sensitive Na<sup>+</sup> channel (*SLC12A3*), while *WNK1* is a negative regulator of *WNK4*. *WNK1* also activates NCC (*SLC12A3*), ENaC (*SCNN1A*, *SCNN1B*, *SCNN1G*, *SCNN1D*), and inhibits the renal K<sup>+</sup> channel ROMK (*KCNJ1*) (52,53). Under hyperosmotic or hypotonic low-Cl<sup>−</sup> conditions, WNK isoforms are activated, and subsequently phosphorylate and activate the related protein kinases SPAK (*STK39*) and OSR1 (*OXSRI1*) (54). SPAK and OSR1 phosphorylate and activate ion cotransporters that include NCC, NKCC1 (*SLC12A2*) and NKCC2 (*SLC12A1*), which are targets for the commonly thiazide-diuretic and loop-diuretic drugs, the former being an excellent antihypertensive drug (55).

ENaC is an important molecular target of aldosterone, which plays a central role in Na<sup>+</sup> homeostasis by controlling Na<sup>+</sup> reabsorption in the aldosterone-sensitive distal nephron. Under basal conditions, ENaC-α (*SCNN1A*) gene transcription is constrained, but can be induced by aldosterone and other stimuli such as serum- and glucocorticoid-induced kinase-1 (*SGK1*) even in the absence of steroids (56,57). *SGK1* can rapidly promote increased apical density of ENaC channels by disinhibiting Nedd4-2 (*NEDD4L*)-triggered internalization and degradation of ENaC subunits (58). The mechanisms underlying this basal repression of *SCNN1A* and its release during gene induction have not yet been established, but there are indications of epigenetic regulation involving combinatorial interactions of Dot1a, the DNA-binding protein Af9, and *SGK1* (59), which regulate histone H3 Lys-79 methylation of chromatin associated with the *SCNN1A* promoter and suppress its transcriptional activity. Aldosterone can disrupt this nuclear complex and result in histone H3 Lys-79 hypomethylation at specific subregions and de-repression of the *SCNN1A* promoter. Histone modification has been shown to play an important role in epigenetic modulation of *WNK4* transcription, contributing to the development of salt-sensitive HTN. Isoproterenol-induced transcriptional suppression of the *WNK4* gene was shown to be mediated via inhibition of histone deacetylase-8 activity (*HDAC8*) in the promoter region of the *WNK4* gene (60) which in turn can stimulate NCC, implying that sympathetic nerve activity can increase BP partly by activating NCC.

## GENETIC BASIS OF MONOGENIC HTN

The monogenic forms of HTN are usually associated with volume expansion and low plasma renin activity secondary to salt retention (39) (Figure 7.1).

- Glucocorticoid-remediable aldosteronism, or familial hyperaldosteronism type 1 (OMIM #103,900) is an autosomal dominant syndrome in which HTN is caused by increased aldosterone secretion driven by adrenocorticotrophic hormone (ACTH). The fusion of the 5' regulatory sequences of 11β-hydroxylase (*CYP11B1*) (which confers ACTH responsiveness) with the distal coding sequences of aldosterone synthase (*CYP11B2*) leads to a chimeric gene which results in

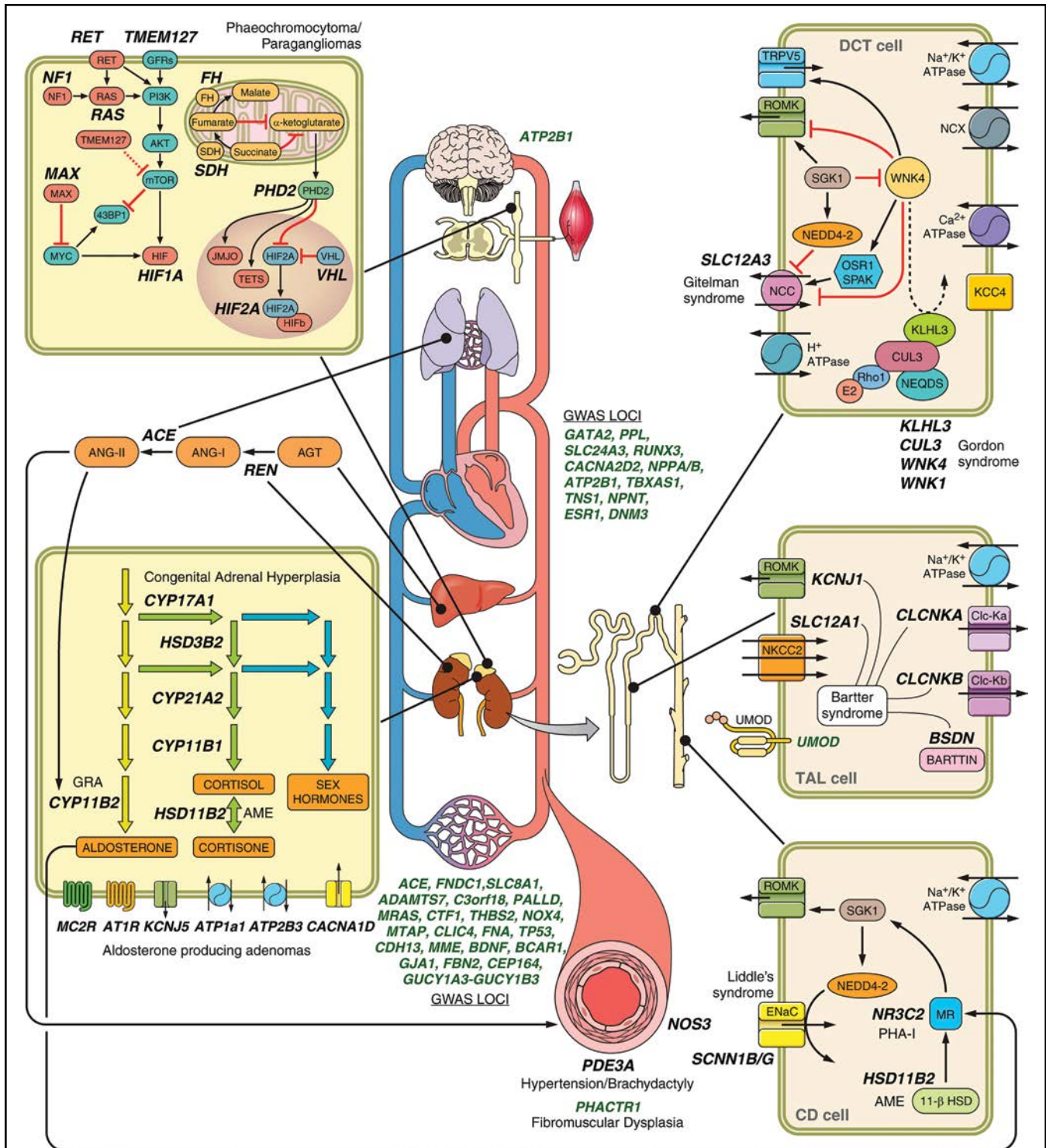


**Figure 7.1** Mutations altering blood pressure in humans and GWAS loci linked to plausible genes. The figure shows the circulatory system and pathways that modulate blood pressure containing genes with known mutations that cause monogenic high or low blood pressure syndromes. In addition, plausible genes linked GWAS loci are shown based on multiple lines of evidence (eQTL or nonsynonymous SNPs or genome-wide 3D proximity maps). (Reprinted with permission from Padmanabhan S, Joe B. *Physiol Rev* 2017; 97(4): 1469–1528.)



ACTH becoming the main controller for aldosterone secretion instead of angiotensin II or potassium (61). It is characterised by early-onset HTN, hyperaldosteronism, variable hypokalaemia, low plasma renin activity (PRA), and abnormal production of 18-oxo-cortisol and 18-hydroxycortisol. Low-dose glucocorticoids to suppress ACTH secretion, or amiloride to directly block the epithelial sodium channel (ENaC), or spironolactone to block binding of aldosterone to the mineralocorticoid receptor (MR) are the specific treatment options for HTN in these individuals.

- Familial hyperaldosteronism type 2 (FH II) (OMIM #605,635) is an autosomal dominant syndrome due to hyperplasia or adenoma of the aldosterone-producing adrenal cortex (APA). The genetic abnormality causing FH-II has been localized to chromosome 7p22 (62), though the causative gene has not yet been identified. FH II is not suppressible by dexamethasone. Adrenalectomy is performed in cases of APA, and medical therapy with aldosterone antagonists in cases of bilateral adrenal hyperplasia. In cases of severe and/or resistant HTN, additional antihypertensive medication is required.
- Apparent mineralocorticoid excess (AME) (OMIM #218,030) is another low-renin HTN syndrome accompanied by hypokalaemia and metabolic alkalosis. The main defect in AME is absence or reduced activity of 11 $\beta$ -hydroxysteroid dehydrogenase (*HSD11B2*), resulting in HTN in which cortisol acts as if it were a potent mineralocorticoid (63). Normally, both cortisol and aldosterone have MR agonist activity and *HSD11B2* is protective by metabolising cortisol to prevent its binding to the MR. A serine to leucine mutation in the MR (S810L) results in gain of function leading to severe early-onset HTN, and HTN during pregnancy. One possible mechanism is that cortisone, the main metabolite of cortisol in the kidney, can activate the mutation, conferring a potential permanent increase in renal sodium reabsorption (64,65). AME is usually diagnosed within the first years of life and is characterized by polyuria and polydipsia, failure to thrive, severe HTN with low renin and aldosterone levels, profound hypokalaemia with metabolic alkalosis and most often nephrocalcinosis. Detection of a marked increase (10- to 100-fold) in the ratio of cortisol/cortisone (F/E) or of the tetrahydroxylated metabolites (THF+alloTHF/THE) in plasma and urine is a strong indication for diagnosis. Treatment is usually through blockade of the MR combined with thiazides to normalize BP and reduce hypercalciuria and nephrocalcinosis. Exogenous corticosteroids to block ACTH and suppression of the endogenous secretion of cortisol is also used as a complementary strategy.
- Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders caused by defects in enzymes of cortisol biosynthesis (66). In some of these syndromes, plasma ACTH will increase in an attempt to produce cortisol leading to the accumulation of aberrant products, some of which lead to HTN. Enzyme mutations that are associated with HTN include (in order of frequency): 11 $\beta$ -hydroxylase (OMIM #202,010; *CYP11B1*), 3 $\beta$ -hydroxysteroid dehydrogenase (OMIM #613,890; *HSD3B2*), 17 $\alpha$ -hydroxylase (OMIM #609,300; *CYP17A1*) and cholesterol desmolase (OMIM #118,485; *CYP11A1*). Furthermore, a common SNP near *CYP17A1* has emerged in multiple large BP GWAS meta-analyses (34–37).
- *Aldosterone-producing adenomas (APAs)*: It is estimated that  $\leq 40\%$  of APAs harbour a gain-of-function somatic mutation in a K<sup>+</sup> channel, *KCNJ5*, which results in membrane depolarization and enhanced aldosterone production. Mutations in three other genes have been discovered in a further 7% of APAs – *ATP1A1*, encoding the  $\alpha 1$  subunit of Na<sup>+</sup>/K<sup>+</sup>-ATPase itself; *ATP2B3*, encoding a plasma membrane Ca<sup>2+</sup>-ATPase 3 homologous to the sarcoplasmic endoplasmic reticulum Ca<sup>2+</sup>-ATPases (*ATP2A2*); and *CACNA1D*, encoding an L-type Ca<sup>2+</sup> channel, CaV1.3 (67). The distinction between APA and bilateral hyperplasia is clinically important because removal of the affected adrenal gland in APAs cures or ameliorates HTN in the majority of patients, whereas bilateral adrenal hyperplasia requires lifelong treatment with an aldosterone antagonist and bilateral adrenalectomy is not indicated.

Monogenic low renin HTN syndromes can also be caused by mutations in the renal ion transporters.

- Pseudohypoaldosteronism type II (Gordon syndrome; familial hyperkalaemia; OMIM #145,260) is an autosomal dominant form of HTN characterised by hyperkalaemia, hyperchloremic metabolic acidosis, normal or elevated aldosterone, low renin and normal renal function. Patients under the age of 20 generally have normal BP but then develop HTN in adulthood. Gordon syndrome thus results from either gain-of-function mutations in *WNK1*, or loss-of-function mutations in *WNK4*, and mutations in *Kelch-like 3 (KLHL3)* and *Cullin 3 (CUL3)* genes. Mutations in *WNK1/4* genes lead to increased NaCl reabsorption and decreased potassium secretion. *CUL3* and *KLHL3* mutations putatively inhibit the ubiquitylation of *WNK4*, and probably other WNK isoforms, resulting in the overactivation of NCC/NKCC2 ion cotransporters, and consequently, increased salt retention and HTN. Treatment is based on low-dose thiazide diuretics that are very effective in the correction of HTN, hyperkalaemia and hypercalciuria. Patients with *WNK4* mutations show a better response to thiazide diuretics than those with *WNK1* mutations. They generally do not respond to exogenous mineralocorticoids.
- Liddle syndrome (OMIM # 177,200) is an autosomal dominant condition with a clinical picture of HTN and aldosterone excess, but with very low aldosterone and renin levels. Severe HTN is found in young patients, from infancy to young adulthood (<35 years of age). This is caused by gain-of-function mutations in the genes coding the beta or gamma subunits of ENaC (*SCNN1B*, *SCNN1G*) resulting in deletions of proline-rich regions (68,69). These regions facilitate binding of Nedd4-2 (*NEDD4L*), a regulatory repressor that promotes channel degradation. The inability of beta and gamma subunits to bind Nedd4 results in constitutive expression of sodium channels and prolongs the half-life of ENaCs at the renal distal tubule apical cell surface, inducing sodium reabsorption,

secondary potassium secretion and ultimately, HTN. The clinical picture resembles that of primary hyperaldosteronism but the hormonal profile resembles that of hyporeninism-hypoaldosteronism. Treatment is based on administration of potassium-sparing diuretics, such as amiloride or triamterene, which act by blocking ENaC activity. This results in reduction of BP and correction of hypokalaemia and metabolic alkalosis. Conventional antihypertensive therapies are not effective.

- Bartter (*SLC12A1*, *KCNJ1*, *CLCNKB*, *BSND*, *CaSR*, *CLCK-A*) and Gitelman (*SLC12A3*) syndromes are associated with mutations that reduce salt retention, lower BP and protect against the development of HTN (27,39). Bartter syndrome (OMIM #607,364) patients usually present after the neonatal period with failure to thrive, fatigue, muscle weakness, cramps and carpopedal spasms. Hypokalaemia and alkalosis are common. Mutation in *CLCNKB* gene (1p36), encoding a basolateral chloride channel ClCKb, has been identified as the most frequent cause of classic Bartter syndrome. Both the chloride channels, ClCKa and ClCKb, are expressed in the thick ascending limb (TAL) of the loop of Henle. ClCKa is exclusively expressed in the ascending limb, while ClCKb is also expressed in distal convoluted tubule (DCT). Mutations in *SLC12A1* and *KCNJ1* cause the classic, less severe phenotype. The differential diagnosis includes pseudo-Bartter syndrome (diuretic abuse, surreptitious vomiting), cystic fibrosis, Gitelman syndrome and celiac disease. Treatment includes oral potassium supplements, nonsteroidal anti-inflammatory drugs (e.g. indomethacin) and possibly potassium-sparing diuretics.
- Gitelman syndrome (GS) (OMIM #263,800), also referred to as familial hypokalaemia-hypomagnesemia, is characterized by hypokalaemic metabolic alkalosis in combination with significant hypomagnesemia and low urinary calcium excretion. The prevalence of heterozygotes is approximately 1% in Caucasian populations, making it one of the most frequent inherited renal tubular disorders. Mutations in the solute carrier family12, member 3 gene, *SLC12A3*, which encodes the thiazide-sensitive NaCl cotransporter (NCC), are found in the majority of GS patients. At present, more than 140 different NCC mutations throughout the whole protein have been identified. In a small minority of GS patients, mutations in the *CLCNKB* gene, encoding the chloride channel ClC-Kb, have been identified. Symptoms do not appear before the age of 6 years, and the disease is usually diagnosed during adolescence or adulthood. BP is lower than that in the general population. Most asymptomatic patients with GS remain untreated. Lifelong supplementation of magnesium (magnesium oxide and magnesium sulphate) is recommended. All GS patients are encouraged to maintain a high sodium and high potassium diet.

Resequencing three candidate genes (*SLC12A3*, *SLC12A1*, *KCNJ1*) involved in Bartter and Gitelman syndrome in the Framingham Heart Study population identified 30 distinct potentially deleterious rare mutations present in 49 subjects. In the heterozygous state, these variants were associated with 5.7 mmHg lower BP at age

40 and by 9.0 mmHg at age 60, and in aggregate reduce the risk of HTN by 60% at age 60 (27). This is the first indication that rare variants can produce clinically significant BP reduction in the general population and support the rare-variant-common-disease hypothesis (70,71).

In addition to the kidney, the heart secretes a family of vasodilatory and natriuretic hormones in response to increased wall stress – atrial natriuretic peptide (NPPA) and B-type natriuretic peptide (NPPB). Knockout of one copy of *NPPA* in mice increases BP while overexpression of *NPPA* lowers BP (72,73). There is now convincing evidence for common variations in the *NPPA-NPPB* locus influencing both levels of natriuretic peptides and BP in opposite directions (35–37,74). Furthermore, a SNP near the natriuretic peptide clearance receptor (*NPR3*) also showed genome-wide significant association in European, African and Japanese BP GWAS studies (35,36,75). Interestingly, there is evidence of convergence between studies in animal models of HTN and their emerging signals from BP GWAS analyses (76–78).

A GWAS for HTN using an extreme case-control design identified a SNP in the 5' region of Uromodulin gene (*UMOD*) which is almost exclusively expressed in the thick ascending limb of the loop of Henle in the kidney, identifying a potentially novel pathway of BP regulation through an effect on sodium homeostasis (33). Moreover, independent studies have identified SNPs highly correlated with the HTN SNP near *UMOD* to be associated with chronic kidney disease (79). In *UMOD* knockout mice, there is increased localization of the salt-retaining NKCC2 (sodium-potassium-chloride cotransporter-2) in subapical vesicles of TAL cells with reduced phosphorylation, resulting in reduced cotransporter activity with resulting greater sodium excretion and a 20 mmHg lower BP compared with wild-type mice. Notably, this difference in BP was exacerbated with salt, whereby the knockout mice were resistant to the hypertensive effects of salt (80). Conversely, *UMOD* overexpression was associated with an increase in BP. The main sodium transporter in TAL is NKCC2, which is blocked by the commonly used loop-diuretic furosemide. Trudu et al. (81) showed furosemide treatment significantly enhanced natriuresis and reduced BP levels both in the transgenic mice and in the hypertensive individuals homozygous for the *UMOD* increasing allele.

## AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system maintains cardiovascular homeostasis via pressure, volume, and chemoreceptor signals through three endogenous catecholamines: norepinephrine, epinephrine, and dopamine synthesised in the adrenal medulla (epinephrine) and cytosol of adrenergic neurons. Adrenergic reflexes modulate BP over the short term, and adrenergic function, in concert with hormonal and volume-related factors, contributes to the long-term regulation of arterial pressure. Increased sympathetic nervous system activity has a role in causing HTN (82) which may be the result of background genetic susceptibility interacting with chronic psychogenic stress, obesity or high sodium intake. HTN could also arise or be sustained by defects in baroreceptor function (83). Adrenergic receptors are classified into two types:

- Norepinephrine has more affinity for  $\alpha$  receptors, while epinephrine binds more avidly to  $\beta$  receptors. The  $\alpha_1$  receptors (*ADRA1A*, *ADRA1B*, *ADRA1D*) are located on postsynaptic cells in smooth muscle and elicit vasoconstriction. These receptors are localized on presynaptic membranes of postganglionic nerve terminals and act as negative feedback controllers, inhibiting further norepinephrine release.
- Activation of sinus node and myocardial  $\beta_1$  receptors (*ADRB1*) stimulates the rate and strength of cardiac contraction, respectively, and consequently increases cardiac output.  $\beta_1$  receptor activation also stimulates renin release from the kidney. Activation of  $\beta_2$  receptors (*ADRB2*) by epinephrine relaxes vascular smooth muscle and results in vasodilatation. Hyperinsulinemia may directly stimulate sympathetic activity, in addition to promoting vascular hypertrophy (increased vascular tone), renal sodium retention, increased  $\alpha_1$  adrenergic receptors, and impaired endothelium-dependent vasodilatation. Leptin levels are increased in obese individuals and it may increase BP by stimulation of the sympathetic nervous system (84).

Pheochromocytomas (PCCs) and paragangliomas (PGLs) are rare neuroendocrine tumours of the adrenal glands and the sympathetic and parasympathetic paraganglia (Figure 7.1). Hereditary PGL/PCCs represent 30% of all PGL/PCC, for which prevalence is around 1/500,000 for PCC and 1/1,000,000 for PGL. PCCs and sympathetic PGLs are very similar histologically as well as functionally and cause HTN, which may be either paroxysmal or sustained. PGL can be either hypersecreting (catecholamines) or nonsecreting, and PCCs usually secrete catecholamines. Secreting (sympathetic) PGLs are predominantly found in the thoracic, abdominal and pelvic areas. Hypersecretion manifests as sustained or paroxysmal elevations in BP, headache, episodic profuse sweating, palpitations, pallor and apprehension or anxiety. Up to 10% of genetically determined PCC/PGLs are due to mutations in *SDHD*, *SDHC*, *SDHB*, *SDHA* and *SDHAF2* (or *SDH5*) genes (85). Transmission is autosomal dominant but associated with maternal genomic imprinting for *SDHD* and *SDHAF2* and expressed when the mutation is inherited from the father. Tumours in patients with *SDHB* mutations are more likely to become malignant (86). In contrast to nonhereditary PCC/PGL, hereditary PCC/PGL tends to present at younger ages, to be multifocal, bilateral and recurrent, or to have multiple synchronous neoplasms. Autosomal dominantly inherited PCCs are due to a variety of *RET* proto-oncogene mutations. Other PCC-susceptibility genes include *RET* (multiple endocrine neoplasia syndrome type 2 [MEN-2]), the tumour suppressor gene *VHL* observed in families with von Hippel-Lindau syndrome, and the gene that encodes succinate dehydrogenase subunit B and D (*SDHB*, *SDHD*) which causes familial PGL (85). Treatment for secreting tumours involves BP control with alpha-blockers followed by surgery by specialized teams. If the tumours have not metastasized, surgical resection can be curative. Follow-up is required due to the risk of recurrence and malignancy, in particular for *SDHB* mutation-carriers. For head and neck PGL, external radiotherapy is recommended.

While none of these targets were evident on primary GWAS analyses, post hoc analysis investigating 30 genes encoding known antihypertensive drug targets identified a SNP near *ADRB1* which attained genome-wide significance (87).

## VASCULAR MECHANISMS

Vascular diameter and compliance of resistance arteries are important determinants of arterial pressure. Vascular changes in HTN may result from either abnormal extracellular stimuli or an altered intracellular signalling cascade leading to enhanced vasoconstriction, blunted vasodilation and vascular wall hypertrophy/remodelling, all of which contribute to elevated peripheral vascular resistance. The humoral factors that regulate arteries in HTN are:

- Vasoconstrictor agents such as angiotensin II, endothelin-1, catecholamines and vasopressin; vasodilator agents such as nitric oxide (NO), endothelium-derived hyperpolarizing factor and natriuretic peptides
- Growth factors such as insulin-like growth factor-1, platelet-derived growth factor (PDGF), epidermal growth factor (EGF) and basic fibroblast growth factor
- Cytokines such as transforming growth factor- $\beta$ , tumour necrosis factor and interleukins (88)

Vascular endothelial function also modulates vascular tone. The vascular endothelium synthesizes and releases a spectrum of vasoactive substances, including NO, a potent vasodilator. NO exerts vasodilating and antiproliferative effects on smooth muscle cells and inhibits thrombocyte aggregation and leukocyte adhesion. The synthesis of NO is controlled by the enzyme endothelial NO synthase (*NOS3*) and is induced by calcium-mobilizing agents and fluid shear stress. Other vascular relaxation factors include endothelins and prostacyclin. Endothelin-1 (*EDN1*) activates specific ETA receptors (*EDNRA*) on vascular smooth muscle cells to cause vasoconstriction and cell proliferation. In contrast, endothelial ETB receptors (*EDNRB*) mediate vasodilatation via release of NO and prostacyclin (*PGI2*). GWAS of coronary artery disease (CAD) showed the SNP rs9349379 G allele (frequency 36%) was associated with increased risk of CAD and coronary calcification but decreased risk for four conditions (migraine headache, cervical artery dissection, fibromuscular dysplasia and HTN [89,90]). This SNP is located within the third intron of the gene encoding phosphatase and actin regulatory protein 1 (*PHACTR1*). However, functional analysis of this variant show that it regulates expression of endothelin 1 (*EDN1*), a gene located 600 kb upstream of *PHACTR1*. The CAD risk associated with this allele is likely through increased endothelial production of ET-1 and subsequent binding to the ET<sub>A</sub> receptor, which promotes atherosclerosis. However, the association of the G allele with low systolic BP is thought to be through the action of ET-1 on the second endothelin receptor, ET<sub>B</sub> (91). In contrast to the coronary arteries where ET<sub>A</sub> receptors predominate, ET<sub>B</sub> receptors are more abundant in the large systemic arteries. The protective effect of this allele on BP is explained by action of ET1 on ET<sub>B</sub> receptors which predominate in large vessels. ET-1 binding to ETB triggers endothelium-dependent vasodilation through the production of NO, prostacyclins, and renal natriuresis. Interestingly, variants in the *PHACTR1* gene have been associated with fibromuscular dysplasia (FMD), a nonatherosclerotic vascular disease leading to stenosis, dissection and aneurysm affecting mainly the renal and cerebrovascular arteries



(92). Variants in the gene for vascular endothelial growth factor A (*VEGFA*) which induces proliferation, migration of vascular endothelial cells, and stimulates angiogenesis, is one of the replicated signals from GWAS. The GWAS locus containing urotensin-2 receptor (*UTS2R*) gene encodes a class A rhodopsin family G-protein–coupled receptor that upon activation by the neuropeptide urotensin II produces profound vasoconstriction. One of the GWAS loci is the relaxin gene, which encodes a G-protein–coupled receptor with roles in uterine relaxation, vasorelaxation and cardiac function which signals via phosphatidylinositol 3-kinase (*PI3K*).

Ion transport by vascular smooth muscle cells may contribute to HTN-associated abnormalities of vascular tone and vascular growth, both of which are modulated by intracellular pH. An increased  $\text{Na}^+/\text{H}^+$  exchanger (*SLC9A1*) can stimulate vascular tone and cell growth by increasing sodium reabsorption in renal proximal tubule cells (93). Other ion transporters considered are  $\text{Na}^+$  bicarbonate transporter (*SLC4A10*) and the  $\text{Na}^+$ - $\text{Ca}^{2+}$  exchanger NCX (*SLC8A1*). One hypothesis for the mechanism by which excess salt intake elevates BP is through the observed rise in cardiotoxic steroids such as ouabain in response to salt intake (94). It is believed that ouabain inhibits the plasma membrane  $\text{Na}^+/\text{K}^+$  ATPase, leading to an increase in cytosolic  $\text{Na}^+$  concentration, which raises the cytosolic  $\text{Ca}^{2+}$  concentration through the involvement of the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger NCX (*SLC8A1*) and thereby increases contraction in vascular or heart muscle (95).

## FUTURE DIRECTIONS

Advances in genomics have accelerated over the last decade, leading to an unparalleled leap in our understanding of the genetic architecture of BP and HTN (40). While the technological and analytic aspects of genomics have been very successful in discovering DNA sequence variants associated with BP and HTN, the functional and biological significance of the vast number of these variants in the human genome are unknown. The *UMOD* locus from GWAS is now the basis of a clinical trial (clinicaltrials.gov NCT03354897) to reposition a loop diuretic in the HTN care pathway. Other GWAS loci encoding *MARK3*, *PDGFC*, *TRHR*, *ADORA1*, *GABRA2*, *VEGFA* and *PDE3A* within systems that have existing drugs not currently linked to a known antihypertensive mechanism and may offer repurposing opportunities. Moving from single-locus dissection, newer analytic methods will test the molecular network hypothesis on a genome-wide scale to fully understand the networks of pathways that govern the genotype–BP causality relationship. Another emerging hypothesis for contributions from the genome to complex traits is that alterations in nuclear organization of DNA resulting in higher order structures, such as folds of DNA within chromatin, confer differential susceptibility. Other ‘omics’ technologies such as metabolomics and metagenomics are potentially powerful tools to identify molecular pathways, involvement of the microbiome and environmental factors in influencing the BP phenotype. Thus the future of BP genomics is set to move into the realms of further discovery using novel platforms, functional dissection and validation of pathways in molecular and clinical studies.

## REFERENCES

1. Krousel-Wood MA, Muntner P, He J et al. Primary prevention of essential hypertension. *Med Clin North Am* 2004; 88(1): 223–238.
2. Cordain L, Eaton SB, Sebastian A et al. Origins and evolution of the Western diet: Health implications for the 21st century. *Am J Clin Nutr* 2005; 81(2): 341–354.
3. Neel JV. Diabetes mellitus: A ‘thrifty’ genotype rendered detrimental by ‘progress’? *Am J Hum Genet* 1962; 14(4): 353–362.
4. Konner M, Eaton SB. Paleolithic nutrition: Twenty-five years later. *Nutr Clin Pract* 2010; 25(6): 594–602.
5. Padmanabhan S, Newton-Cheh C, Dominiczak AF. Genetic basis of blood pressure and hypertension. *Trends Genet* 2012; 28(8): 397–408.
6. Burt VL, Whelton P, Roccella EJ et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. *Hypertension* 1995; 25(3): 305–313.
7. Barker DJ, Eriksson JG, Forsén T et al. Fetal origins of adult disease: Strength of effects and biological basis. *Int J Epidemiol* 2002; 31(6): 1235–1239.
8. Nakajima T, Wooding S, Sakagami T et al. Natural selection and population history in the human angiotensinogen gene (*AGT*): 736 complete *AGT* sequences in chromosomes from around the world. *Am J Hum Genet* 2004; 74(5): 898–916.
9. Weder AB. Evolution and hypertension. *Hypertension* 2007; 49(2): 260–265.
10. Young JH, Chang YP, Kim JD et al. Differential susceptibility to hypertension is due to selection during the out-of-Africa expansion. *PLOS Genet* 2005; 1(6): e82.
11. Brunner H, Gavras H. Is the renin system necessary? *Am J Med* 1980; 69(5): 739–745.
12. Mongeau J.-G, Biron P, Sing CF. The influence of genetics and household environment upon the variability of normal blood pressure: The Montreal Adoption Survey. *Clin Exp Hypertens A* 1986; 8(4–5): 653–660.
13. Harrap SB, Stebbing M, Hopper JL et al. Familial patterns of covariation for cardiovascular risk factors in adults: The Victorian Family Heart Study. *Am J Epidemiol* 2000; 152(8): 704–715.
14. Hunt SC, Williams RR, Barlow GK. A comparison of positive family history definitions for defining risk of future disease. *J Chronic Dis* 1986; 39(10): 809–821.
15. Bochud M, Bovet P, Elston RC et al. High heritability of ambulatory blood pressure in families of East African descent. *Hypertension* 2005; 45(3): 445–450.
16. Havlik RJ, Garrison RJ, Feinleib M et al. Blood pressure aggregation in families. *Am J Epidemiol* 1979; 110(3): 304–312.
17. Hottenga J.-J, Boomsma DI, Kupper N et al. Heritability and stability of resting blood pressure. *Twin Res Hum Genet* 2005; 8(5): 499–508.
18. Kupper N, Willemsen G, Riese H et al. Heritability of day-time ambulatory blood pressure in an extended twin design. *Hypertension* 2005; 45(1): 80–85.
19. Snieder H, Harshfield GA, Treiber FA. Heritability of blood pressure and hemodynamics in African- and European-American youth. *Hypertension* 2003; 41(6): 1196–1201.
20. Fagard R, Brguljan J, Staessen J et al. Heritability of conventional and ambulatory blood pressures. A study in twins. *Hypertension* 1995; 26(6 Pt 1): 919–924.
21. Fava C, Burri P, Almgren P et al. Heritability of ambulatory and office blood pressure phenotypes in Swedish families. *J Hypertens* 2004; 22(9): 1717–1721.
22. Caulfield M, et al. Genome-wide mapping of human loci for essential hypertension. *Lancet* 2003; 361(9375): 2118–2123.
23. Lander ES. The new genomics: Global views of biology. *Science* 1996; 274(5287): 536–539.
24. Reich DE, Lander ES. On the allelic spectrum of human disease. *Trends Genet* 2001; 17(9): 502–510.
25. Marth G, Schuler G, Yeh R et al. Sequence variations in the public human genome data reflect a bottlenecked population history. *Proc Natl Acad Sci USA* 2003; 100(1): 376–381.
26. Fu W, O’Connor TD, Jun G et al. Analysis of 6,515 exomes reveals the recent origin of most human protein-coding variants. *Nature* 2013; 493(7431): 216–220.
27. Ji W, Foo JN, O’Roak BJ et al. Rare independent mutations in renal salt handling genes contribute to blood pressure variation. *Nat Genet* 2008; 40(5): 592–599.
28. Pickering GW. The genetic factor in essential hypertension\*. *Ann Intern Med* 1955; 43(3): 457–464.

29. Oldham, PD, Pickering G, Fraser Roberts JA et al. The nature of essential hypertension. *The Lancet* 1960; 275(7134): 1085–1093.
30. Guyton AC, Coleman TG, Fourcade JC et al. Physiologic control of arterial pressure. *Bull N Y Acad Med* 1969; 45(9): 811–830.
31. Guyton AC, Coleman TG, Cowley AW Jr et al. Systems analysis of arterial pressure regulation and hypertension. *Ann Biomed Eng* 1972; 1(2): 254–281.
32. Guyton AC, Coleman TG, Granger HJ. Circulation: Overall regulation. *Annu Rev Physiol* 1972; 34: 13–46.
33. Padmanabhan S, Melander O, Johnson T et al. Genome-wide association study of blood pressure extremes identifies variant near UMOD associated with hypertension. *PLOS Genet* 2010; 6(10): e1001177.
34. Levy D, Ehret GB, Rice K et al. Genome-wide association study of blood pressure and hypertension. *Nat. Genet* 2009; 41(6): 677–687.
35. Kato N, Takeuchi F, Tabara Y et al. Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in east Asians. *Nat. Genet* 2011; 43(6): 531–538.
36. Ehret GB, Munroe PB, Rice KM et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature* 2011; 478(7367): 103–109.
37. Newton-Cheh C, Johnson T, Gateva V et al. Genome-wide association study identifies eight loci associated with blood pressure. *Nat Genet* 2009; 41(6): 666–676.
38. Adeyemo A, Gerry N, Chen G et al. A genome-wide association study of hypertension and blood pressure in African Americans. *PLOS Genet* 2009; 5(7): e1000564.
39. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. *Cell* 2001; 104(4): 545–556.
40. Padmanabhan S, Joe B. Towards precision medicine for hypertension: A review of genomic, epigenomic, and microbiomic effects on blood pressure in experimental rat models and humans. *Physiol Rev* 2017; 97(4): 1469–1528.
41. Kraja AT, Cook JP, Warren HR et al. New blood pressure-associated loci identified in meta-analyses of 475,000 individuals. *Circ Cardiovasc Genet* 2017; 10(5).
42. Warren HR, Evangelou E, Cabrera CP et al. Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk. *Nat Genet* 2017; 49(3): 403–415.
43. International Consortium for Blood Pressure Genome-Wide Association Studies, Ehret GB, Munroe PB, Rice KM et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature* 2011; 478(7367): 103–109.
44. Wain LV, Vaez A, Jansen R et al. Novel blood pressure locus and gene discovery using genome-wide association study and expression data sets from blood and the kidney. *Hypertension* 2017. Jul 24. pii: HYPERTENSIONAHA.117.09438. doi: 10.1161/HYPERTENSIONAHA.117.09438. [Epub ahead of print]
45. Rose G, Stamler J, Stamler R et al. Intersalt: An international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *Br Med J* 1988; 297(6644): 319–328.
46. Cutler JA, Follmann D, Allender PS. Randomized trials of sodium reduction: An overview. *Am J Clin Nutr* 1997; 65(2): 643S–651S.
47. Kurtz TW, Morris RC. Dietary chloride as a determinant of 'sodium-dependent' hypertension. *Science* 1983; 222(4628): 1139–1141.
48. Whitescarver SA, Ott CE, Jackson BA et al. Salt-sensitive hypertension: Contribution of chloride. *Science* 1984; 223: 1430–1433.
49. O'Connor W. Normal sodium balance in dogs and in man. *Cardiovasc Res* 1977; 11(5): 375–408.
50. Curtis JJ, Luke RG, Dustan HP et al. Remission of essential hypertension after renal transplantation. *N Engl J Med* 1983; 309(17): 1009–1015.
51. Rettig R, Grisk O. The kidney as a determinant of genetic hypertension. *Hypertension* 2005; 46(3): 463–468.
52. Yang C-L, Angell J, Mitchell R et al. WNK kinases regulate thiazide-sensitive Na-Cl cotransport. *J Clin Invest* 2003; 111(7): 1039.
53. Wilson FH, Disse-Nicodème S, Choate KA et al. Human hypertension caused by mutations in WNK kinases. *Science* 2001; 293(5532): 1107–1112.
54. McCormick JA, Ellison DH. The WNKs: Atypical protein kinases with pleiotropic actions. *Physiol Rev* 2011; 91(1): 177–219.
55. Kahle KT, Rinehart J, Lifton RP. Phosphoregulation of the Na–K–2Cl and K–Cl cotransporters by the WNK kinases. *Biochim Biophys Acta* 2010; 1802(12): 1150–1158.
56. Debonneville C, Flores SY, Kamynina E et al. Phosphorylation of Nedd4-2 by Sgk1 regulates epithelial Na<sup>+</sup> channel cell surface expression. *EMBO J* 2001; 20(24): 7052–7059.
57. Boyd C, Náráy-Fejes-Tóth A. Gene regulation of ENaC subunits by serum- and glucocorticoid-inducible kinase-1. *Am J Physiol Renal Physiol* 2005; 288(3): F505–F512.
58. Flores SY, Loffing-Cueni D, Kamynina E et al. Aldosterone-induced serum and glucocorticoid-induced kinase 1 expression is accompanied by Nedd4-2 phosphorylation and increased Na<sup>+</sup> transport in cortical collecting duct cells. *J Am Soc Nephrol* 2005; 16(8): 2279–2287.
59. Zhang D, Yu ZY, Cruz P et al. Epigenetics and the control of epithelial sodium channel expression in collecting duct. *Kidney Int* 2009; 75(3): 260–267.
60. Mu S, Shimomura T, Ogura S et al. Epigenetic modulation of the renal [beta]-adrenergic-WNK4 pathway in salt-sensitive hypertension. *Nat Med* 2011; 17(5): 573–580.
61. Lifton RP, Dluhy RG, Powers M et al. A chimaeric 11 beta-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. *Nature* 1992; 355(6357): 262–265.
62. Lafferty AR, Torpy DJ, Stowasser M et al. A novel genetic locus for low renin hypertension: Familial hyperaldosteronism type II maps to chromosome 7 (7p22). *J Med Genet* 2000; 37(11): 831–835.
63. Cerame BJ, New MI. Hormonal hypertension in children: 11beta-hydroxylase deficiency and apparent mineralocorticoid excess. *J Pediatr Endocrinol Metab* 2000; 13(9): 1537–1547.
64. Geller DS, Farhi A, Pinkerton N et al. Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. *Science* 2000; 289(5476): 119–123.
65. Rafestin-Oblin M-E, Souque A, Bocchi B et al. The severe form of hypertension caused by the activating S810L mutation in the mineralocorticoid receptor is cortisone related. *Endocrinology* 2003; 144(2): 528–533.
66. New MI, Levine LS. Hypertension of childhood with suppressed renin. *Endocr Rev* 1980; 1(4): 421–430.
67. Fernandes-Rosa FL, Boulkroun S, Zennaro MC. Somatic and inherited mutations in primary aldosteronism. *J Mol Endocrinol* 2017; 59(1): R47–R63.
68. Hansson JH, Nelson-Williams C, Suzuki H et al. Hypertension caused by a truncated epithelial sodium channel  $\gamma$  subunit: Genetic heterogeneity of Liddle syndrome. *Nat Genet* 1995; 11(1): 76–82.
69. Shimkets RA, Warnock DG, Bositis CM et al. Liddle's syndrome: Heritable human hypertension caused by mutations in the beta subunit of the epithelial sodium channel. *Cell* 1994; 79(3): 407–414.
70. Eyre-Walker A. Genetic architecture of a complex trait and its implications for fitness and genome-wide association studies. *Proc Natl Acad Sci USA* 2010; 107(suppl 1): 1752–1756.
71. Pritchard JK. Are rare variants responsible for susceptibility to complex diseases? *Am J Hum Genet* 2001; 69(1): 124–137.
72. John SW, Krege JH, Oliver PM et al. Genetic decreases in atrial natriuretic peptide and salt-sensitive hypertension. *Science* 1995; 267(5198): 679.
73. Schillinger KJ, Tsai SY, Taffet GE et al. Regulatable atrial natriuretic peptide gene therapy for hypertension. *Proc Natl Acad Sci U S A* 2005; 102(39): 13789–13794.
74. Newton-Cheh C, Larson MG, Vasan RS et al. Association of common variants in NPPA and NPPB with circulating natriuretic peptides and blood pressure. *Nat Genet* 2009; 41(3): 348–353.
75. Zhu X, Young JH, Fox E et al. Combined admixture mapping and association analysis identifies a novel blood pressure genetic locus on 5p13: Contributions from the CARE consortium. *Hum Mol Genet* 2011; 20(11): 2285–2295.
76. Brosnan MJ, Clark JS, Jeffs B et al. Genes encoding atrial and brain natriuretic peptides as candidates for sensitivity to brain ischemia in stroke-prone hypertensive rats. *Hypertension* 1999; 33(1): 290–297.
77. Jeffs B, Clark JS, Anderson NH et al. Sensitivity to cerebral ischemic insult in a rat model of stroke is determined by a single genetic locus. *Nat Genet* 1997; 16(4): 364–367.
78. Ye P, West MJ. Cosegregation analysis of natriuretic peptide genes and blood pressure in the spontaneously hypertensive rat. *Clin Exp Pharmacol Physiol* 2003; 30(12): 930–936.
79. Köttgen A, Glazer NL, Dehghan A et al. Multiple loci associated with indices of renal function and chronic kidney disease. *Nat Genet* 2009; 41(6): 712–717.

80. Graham LA, Padmanabhan S, Fraser NJ et al. Validation of uromodulin as a candidate gene for human essential hypertension. *Hypertension* 2014; 63(3): 551–558.
81. Trudu M, Janas S, Lanzani C et al. Common noncoding UMOD gene variants induce salt-sensitive hypertension and kidney damage by increasing uromodulin expression. *Nat Med* 2013; 19(12): 1655–1660.
82. Esler M, Rumanitir M, Kaye D et al. The sympathetic neurobiology of essential hypertension: Disparate influences of obesity, stress, and noradrenaline transporter dysfunction? *Am J Hypertens* 2001; 14(S3): 139S–146S.
83. Izzo JL, Taylor AA. The sympathetic nervous system and baroreflexes in hypertension and hypotension. *Curr Hypertens Rep* 1999; 1(3): 254–263.
84. Kalil GZ, Haynes WG. Sympathetic nervous system in obesity-related hypertension: Mechanisms and clinical implications. *Hypertens Res* 2012; 35(1): 4–16.
85. Welander J, Söderkvist P, Gimm O. Genetics and clinical characteristics of hereditary pheochromocytomas and paragangliomas. *Endocr Relat Cancer* 2011; 18(6): R253–R276.
86. van Hulsteijn LT, Dekkers OM, Hes FJ et al. Risk of malignant paraganglioma in SDHB-mutation and SDHD-mutation carriers: A systematic review and meta-analysis. *J Med Genet* 2012; 49(12): 768–776.
87. Johnson AD, Newton-Cheh C, Chasman DI et al. Association of hypertension drug target genes with blood pressure and hypertension in 86,588 individuals. *Hypertension* 2011; 57(5):903–910.
88. Touyz RM. Intracellular mechanisms involved in vascular remodelling of resistance arteries in hypertension: Role of angiotensin II. *Exp Physiol* 2005; 90(4): 449–455.
89. Nikpay M, Goel A, Won HH et al. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet* 2015; 47(10): 1121–1130.
90. Gupta RM, Hadaya J, Trehan A et al. A genetic variant associated with five vascular diseases is a distal regulator of endothelin-1 gene expression. *Cell* 2017; 170(3): 522–533 e15.
91. Wellcome Trust Case Control Consortium et al.. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007; 447(7145): 661–678.
92. Kiando SR, Tucker NR, Castro-Vega LJ et al. PHACTR1 is a genetic susceptibility locus for fibromuscular dysplasia supporting its complex genetic pattern of inheritance. *PLOS Genet* 2016; 12(10): e1006367.
93. Xiang M, Feng M, Muend S et al. A human Na<sup>+</sup>/H<sup>+</sup> antiporter sharing evolutionary origins with bacterial NhaA may be a candidate gene for essential hypertension. *Proc Natl Acad Sci USA* 2007; 104(47): 18677–e1018681.
94. Blaustein MP. Physiological effects of endogenous ouabain: Control of intracellular Ca<sup>2+</sup> stores and cell responsiveness. *Am J Physiol Cell Physiol* 1993; 264(6): C1367–C1387.
95. Iwamoto T, Kita S, Zhang J et al. Salt-sensitive hypertension is triggered by Ca<sup>2+</sup> entry via Na<sup>+</sup>/Ca<sup>2+</sup> exchanger type-1 in vascular smooth muscle. *Nat Med* 2004; 10(11): 1193–1199.



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# OXIDATIVE STRESS, INFLAMMATION, IMMUNE SYSTEM AND HYPERTENSION

8

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## INTRODUCTION

Oxidative stress and low-grade subclinical chronic inflammation are interdependent processes that play an important role in pathophysiological mechanisms underlying hypertension (1). These processes are also involved in hypertension-associated target-organ damage, especially of the heart, kidneys, brain, eye and vasculature (2). Normally an acute inflammatory response is a beneficial or protective reaction to an injurious stimulus. However, chronically, inappropriate immune responses and uncontrolled inflammation lead to cell and tissue destruction. In the cardiovascular system, this leads to inflammation and fibrosis, important in hypertension pathophysiology.

Inflammatory cells release reactive oxygen species (ROS) at the site of inflammation increasing oxidative stress, which promotes oxidative injury and cell death (3). ROS also play a critical role in mediating intracellular redox-dependent signalling, further influencing inflammation through stimulatory effects on transcription factors inducing proinflammatory gene expression (4). Chronic inflammation may be considered a consequence of immune dysregulation. Pro-inflammatory cells, especially neutrophils, monocytes and macrophages, contribute to the initiation and persistence of cardiovascular and renal injury and fibrosis in hypertension (5).

Monocytes and macrophages are highly plastic cells and their activation and phenotypic differentiation are influenced by their microenvironment and local factors (6,7). Monocytes are formed in the bone marrow from hematopoietic precursors and enter the circulation via CCR2 receptor stimulation. They have a relatively short half-life in the circulation and are recruited to sites of injury where they mature into macrophages. Macrophages in turn differentiate into classically activated M1 or alternatively activated M2 phenotypes (8). M1 macrophages are activated by proinflammatory T-helper (Th)-1 cells as well as antigen-presenting cells, and produce ROS and inflammatory cytokines, including TNF $\alpha$ , interleukin (IL)-1 $\beta$ , IL-12 and IL-23 (9). M2 macrophages are activated by Th2 cytokines, including IL-4 and IL-13 or by anti-inflammatory mediators, such as IL-10 and glucocorticoids (10). Activated M2

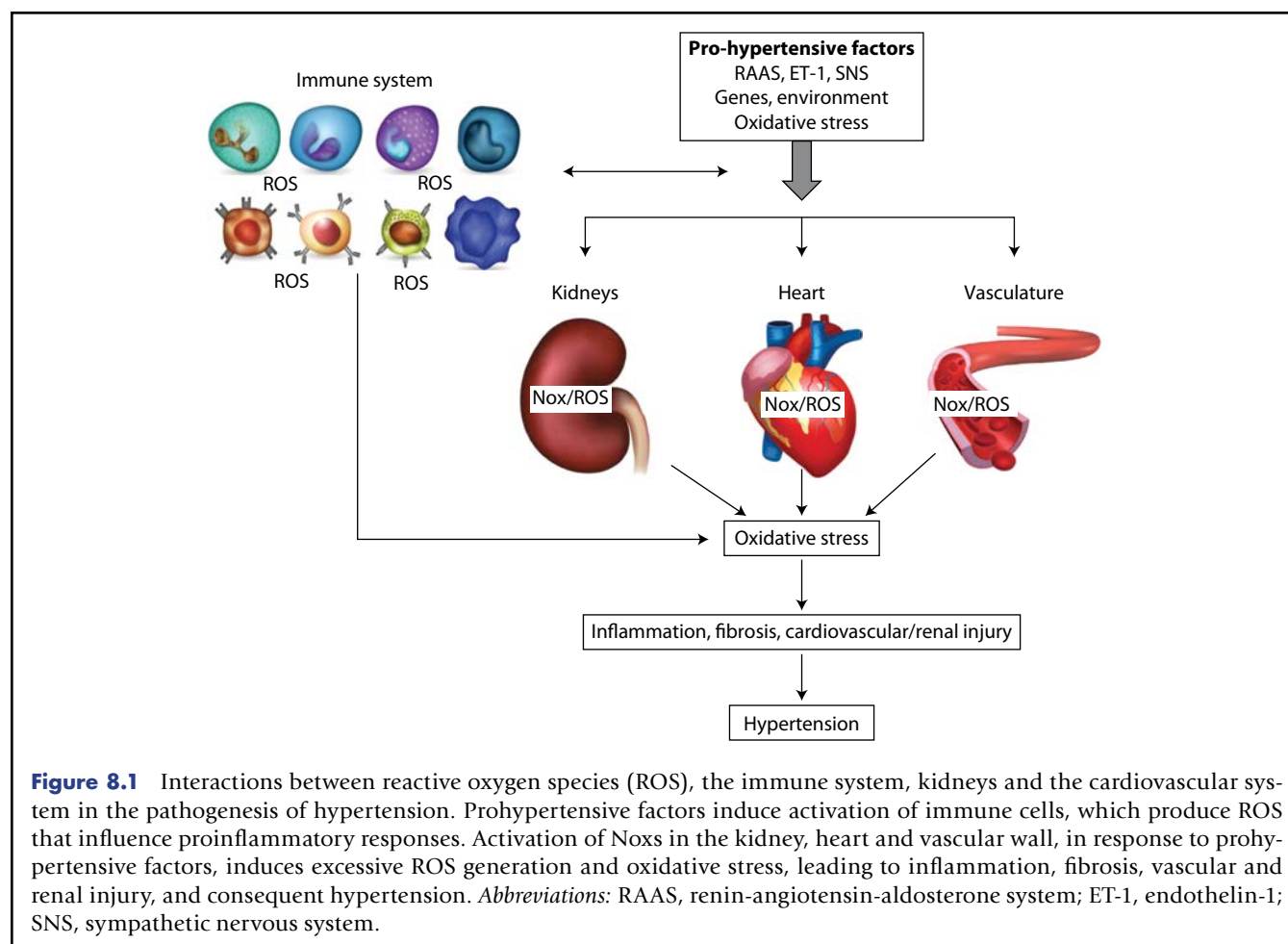
macrophages stimulate arginase activity and mannose receptor (CD206) expression, thereby promoting tissue healing and inhibition of Th-1 cellular responses. In pathological conditions M2 macrophages may be dysregulated, contributing to altered extracellular matrix organisation and fibrosis (11). When inflammation is persistent and chronic, such as in hypertension, monocyte-derived macrophages as well as resident macrophages produce excessive ROS and inflammatory cytokines (IL1 $\beta$  and TNF $\alpha$ ) and chemokines leading to oxidative stress and recruitment of various innate and adaptive immune cell populations into the vascular wall, thereby further amplifying the inflammatory environment (11,12). An important trigger in vascular inflammation in hypertension is endothelial activation and oxidative stress.

## IMPORTANCE OF ROS IN HYPERTENSION

The relationship between ROS, immune cells and hypertension is complex because ROS are important mediators of immune cell function while at the same time are also activators of the immune system in hypertension (12,13) (Figure 8.1). Under physiological conditions ROS regulate normal cellular signalling involved in cell growth, differentiation, repair and ageing (14). ROS are also critically involved in host-defence responses through activation of immune cells (15). In pathological conditions, increased production of vascular ROS, from resident macrophages, immune and vascular cells, causes endothelial dysfunction, arterial hypertrophy and remodelling, vascular inflammation, capillary rarefaction and altered vascular tone, important processes contributing to vascular damage and target-organ damage in hypertension (16,17).

The key ROS and reactive nitrogen species (RNS) involved in signal transduction, immune activation and cardiovascular biology are superoxide anion (O $_2^-$ ), hydrogen peroxide (H $_2$ O $_2$ ) and nitric oxide (NO) (18). The signalling actions of ROS depend on the subcellular site of production, the type of species generated, proximity to





redox-sensitive signalling molecules, association with antioxidant molecules and local concentration of ROS. Among the many ROS,  $\text{H}_2\text{O}_2$  is especially important in signalling because it is cell membrane permeable, stable and has a longer half-life than  $\text{O}_2^-$  (19).

ROS influence cell function by modifying protein activity through post translational modifications. Briefly, proteins that contain cysteine residues are highly sensitive to oxidative changes that cause alterations in structure, activity and function of downstream target proteins (20). Proteins that are redox sensitive include ion transporters, receptors, signalling molecules, kinases, phosphatases, transcription factors, structural proteins and matrix metalloproteases (MMP), all of which are important in regulating endothelial and vascular smooth muscle cell function as well as cells of the heart and kidney (21). ROS also stimulate production of vasoactive agents, such as angiotensin II (Ang II), endothelin-1 (ET-1) and prostanoids and they regulate intracellular calcium homeostasis, critically involved in triggering and maintaining vasoconstriction and cardiac contraction. In the endothelium,  $\text{H}_2\text{O}_2$  acts as a vasodilator and has been considered to be an endothelium-derived relaxing factor, effects that are mediated in part through activation of  $\text{PKG1}\alpha$  and posttranslational modifications involving S-glutathionylation (22,23). ROS stimulate activation of transcription factors and proinflammatory genes, chemokine and cytokine production and recruitment and activation of inflammatory and immune cells that promote cardiovascular and renal inflammation and fibrosis (16,17).

## PRODUCTION OF ROS IN THE CARDIOVASCULAR SYSTEM

In cardiac, vascular and renal cells ROS are produced primarily by nonphagocytic nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (Nox), although other enzymatic sources may also contribute, such as xanthine oxidase, mitochondrial electron transport chain, uncoupled endothelial nitric oxide synthases (eNOS), cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 oxidases (24). In hypertension Noxs appear to be most important in the vasculature. Immune cells and resident macrophages also contribute to vascular oxidative stress and inflammation by generating  $\text{O}_2^-$  through the prototype phagocytic NADPH oxidase, Nox2 (also termed gp91phox-containing NADPH oxidase).

## NONPHAGOCYTIC NOXS IN THE CARDIOVASCULAR SYSTEM

The main function of Nox enzymes is the production of ROS, and accordingly Noxs are called 'professional oxidases', unlike other oxidases that generate  $\text{O}_2^-$  as by-products of enzymatic activity. Nox catalyzes the reduction of  $\text{O}_2$  by NADPH, as the electron donor, thereby generating  $\text{O}_2^-$ . Seven Nox isoforms have been identified (Nox1-5, Duox1, Duox2) of which Nox 1, 2, 4, and 5 are present in human



vascular, cardiac and renal cells (25,26). Nox1, Nox2 and Nox4 are regulated by binding to various NADPH oxidase subunits, including p22phox, p47phox (isoform, NOXO1), p67phox (isoform, NOXA1) and p40phox, whereas Nox5 does not require any subunits for its activation (27). Vascular Nox activity is increased in hypertension and is highly sensitive to prohypertensive factors such as Ang II, ET-1, aldosterone and mechanical stretch. In vascular smooth muscle and endothelial cells from resistance arteries of hypertensive patients, expression of Noxs and ROS generation are increased (28,29). These processes are associated with oxidative stress and altered redox signalling through kinases and phosphatases leading to endothelial dysfunction and vascular remodelling. Activation of proinflammatory transcription factors by ROS promotes vascular inflammation. Cardiac Nox4 has been shown to have both cardioprotective and cardioinjurious effects in experimental models of heart disease (30,31), while renal Nox4 appears to be important in diabetic nephropathy (32). Vascular Nox1 has been associated with atherosclerosis (33).

### NOX-DERIVED ROS, ANTIOXIDANT ENZYMES AND HYPERTENSION

The importance of Nox-derived ROS in the pathophysiology of hypertension has been demonstrated mainly in transgenic mouse models in which genes for Nox isoforms or NADPH oxidase subunits have been deleted or overexpressed (34). In mice that overexpress Nox1 or p22phox, Ang II-induced hypertension is augmented, with associated endothelial dysfunction and vascular remodelling and inflammation. In DOCA-salt hypertension, renal Nox4 is important. In mice expressing human Nox5 in a podocyte-specific manner, baseline blood pressure is increased and renal function is altered. Mice deficient in p47phox or Nox1 appear to be protected against Ang II-induced hypertension (35). The role of Noxs in human hypertension awaits clarification, but vascular Nox5 expression and associated ROS production are increased in patients with hypertension, atherosclerosis and ischaemic heart disease.

### ANTIOXIDANT ENZYMES

To maintain cellular redox status, a number of antioxidant systems have evolved to prevent excessive ROS accumulation and to protect against oxidative damage (36). In particular, vascular cells possess functionally active superoxide dismutase (SOD), catalase, peroxidases, glutathione and thioredoxin. SOD, of which there are three isoforms, are especially important because they catalyze dismutation of  $O_2^-$  to  $H_2O_2$  and localize in specific cellular compartments: cytosol for SOD1, mitochondria for SOD2 and extracellular matrix for SOD3. As such, SOD influences vascular redox signalling in a controlled and compartmentalized function.

Antioxidants are regulated by transcriptional modulators such as nuclear factor-erythroid 2 p45-related factor (Nrf-2) and DJ-1. Nrf-2 is a transcription factor that binds to the antioxidant response element of many genes and is activated when oxidative stress is increased. DJ-1 has antioxidant properties and also has cytoprotective effects by regulating redox signalling through ERK1/2 and ASK1.

### NUCLEAR FACTOR-ERYTHROID 2 P45-RELATED FACTOR TRANSCRIPTION FACTOR

Nrf-2 is the master regulator of antioxidants through its control of genes that contain antioxidant response element (ARE) (37). Nrf-2 induces transcriptional activation of antioxidant genes containing ARE, including glutathione peroxidases, heme oxygenase-1, thioredoxin reductase, glutathione-S-transferase, and SOD (38). Nrf2 is constitutively controlled by ROS and by repressor protein Kelch-like ECH-associated protein 1 (Keap1) and increases antioxidant defence mechanisms in conditions of oxidative stress and cell stress. In rodent models of hypertension Nrf-2 activity is reduced, oxidative stress is increased and redox-sensitive vascular function is impaired (38). These phenomena are reversed with Nrf2 activators, bardoxolone and L-sulforaphane. Treatment of DOCA-salt rats with epicatechin, another Nrf-2 activator, decreased blood pressure (39).

### DJ-1 AND HYPERTENSION

DJ-1 is a multifunctional ROS-responsive protein that acts both as an antioxidant and signalling molecule (40). It has been implicated in the differentiation of mesenchymal stem cells into smooth muscle cells (41) and hence may be important in vascular structural changes in hypertension. DJ-1 has also been shown to have vasoprotective effects by inhibiting TGF $\beta$ /Smad signalling and preventing Nrf2 degradation (42). DJ-1 deficiency has been associated with hypertension and seems to be especially important in modulating oxidative stress in the kidney in experimental models of dopamine-associated hypertension (43).

### ROS AND HUMAN HYPERTENSION

Clinical studies in patients with hypertension demonstrated that systolic and diastolic blood pressure correlate positively with biomarkers of oxidative stress and negatively with antioxidant levels (44,45). Population-based observational studies reported an inverse relationship between various plasma antioxidants and blood pressure. Endothelial dysfunction, a hallmark of vascular injury in hypertension, is associated with increased vascular ROS production, oxidative stress, immune cell activation, increased M1/M2 macrophage expression and vascular inflammation (45,46). This is evidenced by an inverse association between acetylcholine-dependent vasodilation and plasma levels of TBARS and positive associations with serum levels of antioxidants, such as selenium, vitamin C, glutathione peroxidase and SOD activities (46). ROS production in vascular smooth muscle cells from arteries of patients with hypertension demonstrated higher levels of  $O_2^-$  and  $H_2O_2$ , enhanced Ang II-stimulated redox signalling and inflammatory responses compared with cells from normotensive counterparts.

Decreased antioxidant activity (SOD, catalase) and reduced levels of ROS scavengers (vitamin E, glutathione) may contribute to oxidative stress in human hypertension (46). Plasma vitamin C levels are inversely related to blood pressure in normotensive and hypertensive cohorts and

are associated with decreased risk for heart failure (46,47). Clinical studies in Japanese women showed a positive association between serum DJ-1 levels and improvements in metabolic syndrome (48).

Causes of perturbed redox status in hypertension are unclear but may relate in part to genetic factors. Polymorphisms in glutathione-S-transferase (intracellular antioxidant enzyme) and the risk of essential hypertension has been demonstrated (49). Polymorphisms have also been shown in NADPH oxidase subunits in hypertensive patients. Individuals with p22phox polymorphisms exhibit altered Nox activity and increased ROS production in human cardiovascular disease. More recently, GWAS data from over 450,000 individuals identified Nox4 and Nox5 as novel blood pressure-related genes (50).

### ROS – THE LINK BETWEEN INFLAMMATION, IMMUNITY AND HYPERTENSION

ROS play a pivotal role in linking the immune system, inflammation and hypertension. Immune cells produce  $O_2^-$  and  $H_2O_2$ , which promote inflammation. Almost every cell type involved in innate and adaptive immunity has been suggested to be involved in the pathophysiology of hypertension. Chronic subclinical, low-grade inflammation involves ROS production by innate immune cells, leading to oxidative stress, causing vascular and renal dysfunction in hypertension. The importance of the innate immune system in hypertension was demonstrated in mice deficient in macrophage colony stimulating factor (M-CSF), an important hematopoietic growth involved in maturation of myeloid cell populations (51). In these mice, which have a reduced number of macrophages, Ang II-induced hypertension is attenuated, and vascular dysfunction is ameliorated. These cardiovascular protective effects are associated with reduced oxidative stress and decreased inflammation. Effector T cells, especially Th-1 and Th-17, and regulatory lymphocytes, which are part of the adaptive immune system, have been identified in the kidneys and vascular wall in experimental and clinical hypertension (52). Recent studies indicate that subsets of T cells express the mineralocorticoid receptor, important in hypertension pathophysiology (53,54). Regulatory T cells (Tregs) suppress immune response activation and inflammation through immunosuppressive cytokines, including TGF- $\beta$ , IL-10, IL-35 and modulation of cAMP levels in target cells (52). Activated B cells produce antibodies that also have been implicated in hypertension. In Ang II-induced hypertension, the number of activated B cells and plasma cells is increased. When B cells are depleted with a CD20 antibody, Ang II-induced hypertension is blunted (55,56). In pulmonary hypertension, lung vascular remodelling is associated with B-cell activation induced by IL-6 produced by mast cells (57).

### THE IMMUNE SYSTEM IN HYPERTENSION

An increasing number of studies have addressed the role of innate and adaptive immunity in cardiovascular disease, revealing a new paradigm that includes the active

participation of macrophages and immune-competent cells (particularly different subsets of lymphocytes) in the mechanisms associated with the pathophysiology of hypertension (58,59) (Figure 8.1).

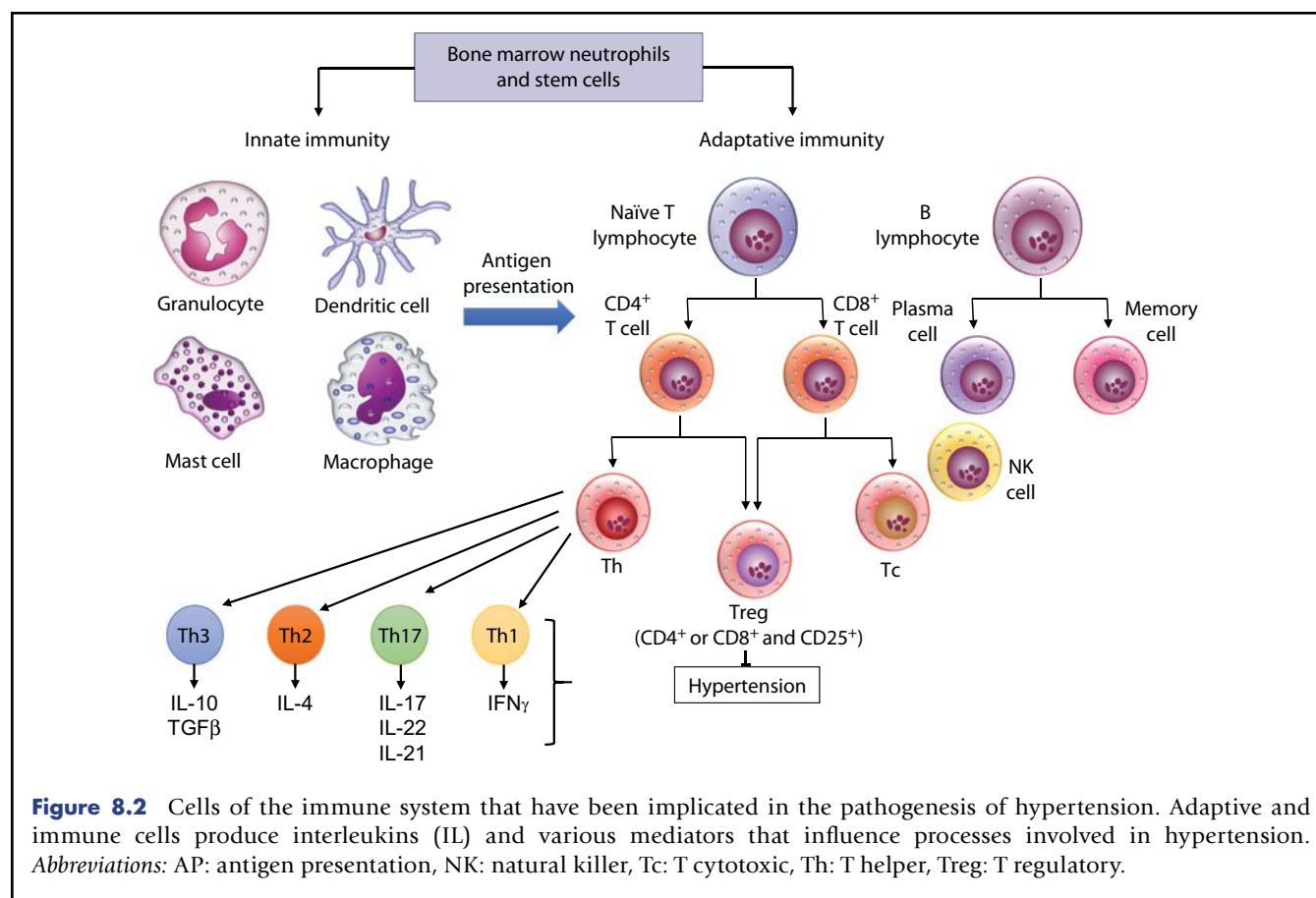
Participation of the innate and the adaptive immune response in mechanisms that contribute to inflammation in cardiovascular disease has been reported in atherosclerosis (58) and hypertension (59,60). Circulating and tissue leukocytes/macrophages are important players in the inflammatory response. However, it seems that some T-lymphocyte subpopulations are involved in the development of high blood pressure, endothelial dysfunction and vascular remodelling (61,62). Subsets of T lymphocytes, either effector T cells, such as Th-1 (interferon- $\gamma$ -producing), Th2 lymphocytes (producing interleukin-4, and Th17 (producing interleukin-17), as well as T suppressor lymphocytes, such as Tregs, which express the transcription factor Forkhead box P3 (Foxp3), may play critical roles in the development of hypertension induced by Ang II infusion or in deoxycorticosterone/salt-sensitive or Dahl salt-sensitive hypertensive rats. In addition, they have been demonstrated to be involved in the progression of vascular remodelling in these models of genetic or experimental hypertension (60,63) (Figure 8.2).

T lymphocyte activation and inflammation are triggered by oxidative stress in hypertension (64,65). Enhanced adaptive immunity arising from a genetic predisposition may underlie vascular inflammation. This may be a consequence of reduced immunosuppressant function of Tregs (60). Infiltrating T cells in the kidney exacerbate renal damage in Ang II-induced hypertension in salt-sensitive rats (56).

Clinical studies demonstrated that T lymphocytes may also be important in the onset of microvascular damage (66). A significant inverse correlation was demonstrated between indices of microvascular structure (media-to-lumen ratio of subcutaneous small arteries and wall-to-lumen ratio of retinal arterioles) and circulating Treg lymphocytes (66). Positive correlations were also observed between the media-to-lumen ratio of subcutaneous small arteries and circulating Th17 lymphocytes (66). A relationship between different subpopulations of circulating CD4<sup>+</sup> T lymphocytes and microvascular or systemic oxidative stress in humans was also observed. Hence some circulating lymphocyte subpopulations may be related to microvascular remodelling through processes involving inflammation, oxidative stress and redox-sensitive proliferation of vascular smooth muscle cells, important in vascular remodelling (67).

Infiltration of immune cells in various organs such as blood vessels, kidney and perivascular adipose tissue is an important component of the inflammatory response leading to cardiovascular damage and hypertension (58–60). How activation of immunity is triggered remains unknown, but neoantigens could be generated by elevated blood pressure through damage-associated molecular pattern receptors (DAMPs) or other unknown mechanisms (60). Once activated, Th1 cells may contribute to blood pressure elevation by affecting the kidney, vascular remodelling of blood vessels via direct effects of the cytokines or through activation of the perivascular adipose tissue (62). On the other hand, Treg cells might protect from blood pressure elevation through immunoprotective mediators.

It has been suggested that adaptive immunity is enhanced due to a genetic predisposition with loci on



chromosome 2, which bears many proinflammatory genes, in hypertensive models such as the Dahl salt-sensitive rat, which exhibits an activated endothelin system (63). The presence of the Brown Norway chromosome 2 on the Dahl salt-sensitive background in the consomic rat (SSBN2) was associated with upregulation of Treg markers and activity, Foxp3 transcription factor expression and production of IL-10 and transforming growth factor (TGF)-β (63). Increased populations of T-lymphocytes and Treg cells in the blood and the spleen were associated with increased blood pressure and vascular inflammation (63). The vasculature of hypertensive rats revealed dysfunctional Treg cells that express low levels of Foxp3b and did not produce immunosuppressive mediators (TGF-β and interleukin-10), thus leading to upregulation of inflammatory responses (63,64). This also influenced vascular structure, since in the aortas of Dahl salt-sensitive rats, wall thickness was increased and preproendothelin-1 levels were increased. These alterations were partially attenuated in consomic rats (63), supporting the notion that Tregs are involved in the development of cardiovascular disease and that T lymphocytes may influence blood pressure (63,64), at least in the models studied.

In Ang II-infused mice lacking T and B cells (RAG-1<sup>-/-</sup> mice), development of hypertension is blunted and vascular remodelling is prevented compared with control C57BL/6 mice. Adoptive transfer of T, but not B, cells restored these abnormalities (65). Moreover, in Ang II-infused mice, adoptive transfer of Tregs, but not of T effector cells, prevented development of hypertension,

oxidative stress and vascular injury, further supporting the idea that immune mechanisms are important in Ang II-dependent hypertension (66–69).

While there is extensive experimental evidence suggesting a role for effector T lymphocytes in the pathophysiology of hypertension, there is a paucity of information in humans (70,71). However, in human hypertension, with ageing, effector lymphocytes may become senescent and lose some of their CD28, leading to blunting of the CD28:CD80/86 costimulation axis, increased surface adhesion molecules and enhanced cytotoxicity (72). In hypertensive patients, circulating levels of interleukin-17A—producing CD4<sup>+</sup> T cells and CD4<sup>+</sup> and CD8<sup>+</sup> T cells that produce interferon-γ were found to be increased compared with normotensive controls (73). In another clinical study, an increase of CD4<sup>+</sup>CD28-IFN-γ<sup>+</sup> Th1 circulating lymphocytes was observed in hypertensive patients, compared with normotensive subjects. This population corresponds to senescent lymphocytes and was previously demonstrated to be increased in some pathological conditions, including atherosclerotic vascular damage (74,75). Therefore, T cells might contribute to human hypertension as suggested by animal studies and may also regulate microvascular function (76).

Th2 lymphocyte subpopulations have been shown to be important in microvascular function and structure, which might influence blood pressure by changes in capillary density. However, the role of Th2 lymphocytes is unclear because these cells have been shown to have both vasoprotective and vaso-injurious effects (77). Some data suggest that Th1 and Th2 lymphocytes have



counterregulatory effects and that the ratio of subtypes of T lymphocytes may be important (78). The Th1/Th2 balance may be crucial for chronic inflammation involved in the initiation and development of hypertensive vascular disease and atherosclerosis (78). Th1 lymphocytes may exert a detrimental role in terms of excessive ROS generation, production of vasoactive cytokines and promotion of inflammation (70,71), which together with blunting of vasoprotective Th2 lymphocytes might contribute to vascular inflammation and damage.

Th17 cells produce IL-17A, which seems to be important in vascular dysfunction and inflammation associated with hypertension (52). Mice deficient in IL-17A have blunted Ang II-induced hypertension and reduced cardiovascular and renal injury compared with Ang II-infused wild-type mice. Moreover, the number of Th17 cells is increased in patients with acute coronary syndrome and unstable carotid atherosclerotic plaques with a significant functional imbalance of Th17/Treg lymphocytes (52,54,79,80). It has also been suggested that a small subset of innate-like T cells expressing the  $\gamma\delta$  T cell receptor could play a role in the initiation of the immune response in hypertension (81).  $\gamma\delta$  T cells mediate Ang II-induced increase in systolic blood pressure, vascular injury and T-cell activation in mice.

The potential clinical relevance of CD4+CD28-  $\gamma$ -IFN-producing T cells in hypertension has recently been highlighted in a study demonstrating that CD4+CD28- T cells can be targeted in vivo in patients with rheumatoid arthritis by using the CD28 co-stimulation blocker CTLA4.Ig (abatacept), resulting in their decrease in the peripheral blood and in the reduction of interferon- $\gamma$  producing Th1 and Th17 T cells seem to be promising in this regard (82).

While different subsets of T lymphocytes have been implicated in the pathogenesis of hypertension and vascular remodeling, the exact mechanisms triggering immune cell activation and recruitment in hypertension remains unclear. However, factors that have been suggested include activation of the sympathetic nervous system, increased interstitial sodium levels, altered mechanical forces, vasoactive agents and activation of the renin-angiotensin-aldosterone system (52,83).

An important study recently highlighted the significance of inflammation, immunity and atherosclerotic vascular disease in clinical medicine. A randomized double-blind trial in over 10,000 patients investigated the effects of canakinumab, a therapeutic monoclonal antibody targeting IL-1 $\beta$ , on nonfatal myocardial infarction, nonfatal stroke or cardiovascular death (CANTOS study). Results demonstrated that anti-inflammatory therapy targeting IL-1 $\beta$ , at a dose of 150 mg every 3 months, resulted in a lower recurrent cardiovascular event versus placebo, independent of lipid lowering. This was associated with reduced levels of proinflammatory markers, IL-6 and C-reactive protein. This large clinical trial provides important evidence that innate immunity can be modulated to reduce cardiovascular risk. Targeting inflammation may be a potentially interesting strategy to reduce atherosclerotic disease. However, whether this approach would also influence blood pressure reduction in hypertension is unknown.

## CONCLUDING REMARKS

In summary, both innate and adaptive immune systems may contribute to the pathogenesis of cardiovascular

disease, vascular remodelling and hypertension (84,85). Fundamental to these processes is increased generation of ROS, decreased NO levels, oxidative damage and inflammation (86,87). However, exactly how immune cells are activated, exactly what their functions are and where they are localized in hypertension still await clarification, especially in the clinical setting. Nevertheless, strategies to normalize immune activation, reduce oxidative stress and manipulate the inflammasome may have therapeutic potential (87), especially in the prevention of vascular injury and target-organ damage associated with hypertension and other cardiovascular diseases.

## REFERENCES

- Guzik TJ, Touyz RM. Oxidative stress, inflammation, and vascular aging in hypertension. *Hypertension* 2017; 70(4): 660–667.
- Incalza MA, D'Oria R, Natalicchio A et al. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. *Vascul Pharmacol* 2018; 100: 1–19.
- Lorenzen I, Mullen L, Bekeschus S, Hanschmann EM. Redox regulation of inflammatory processes is enzymatically controlled. *Oxid Med Cell Longev* 2017; 2017: 8459402.
- Sies H. Hydrogen peroxide as a central redox signaling molecule in physiological oxidative stress: Oxidative eustress. *Redox Biol* 2017; 11: 613–619.
- Franchina DG, Dostert C, Brenner D. Reactive oxygen species: Involvement in T cell signaling and metabolism. *Trends Immunol* 2018; S1471-4906(18): 30016–4.
- Murray PJ. Immune regulation by monocytes. *Semin Immunol* 2017; S1044-5323(17): 30056–8.
- Tabas I, Lichtman AH. Monocyte-macrophages and T cells in atherosclerosis. *Immunity* 2017; 47(4): 621–634.
- Shapouri-Moghaddam A, Mohammadian S, Vazini H et al. Macrophage plasticity, polarization, and function in health and disease. *J Cell Physiol* 2018 January 10. doi: 10.1002/jcp.26429.
- Orihuela R, McPherson CA, Harry GJ. Microglial M1/M2 polarization and metabolic states. *Br J Pharmacol* 2016; 173(4): 649–665.
- Jung M, Ma Y, Iyer RP et al. IL-10 improves cardiac remodeling after myocardial infarction by stimulating M2 macrophage polarization and fibroblast activation. *Basic Res Cardiol* 2017; 112(3): 33.
- Mack M. Inflammation and fibrosis. *Matrix Biol* 2017; 68–69: 106–121.
- Nosalski R, McGinnigle E, Siedlinski M, Guzik TJ. Novel immune mechanisms in hypertension and cardiovascular risk. *Curr Cardiovasc Risk Rep* 2017; 11(4): 12.
- Justin Rucker A, Crowley SD. The role of macrophages in hypertension and its complications. *Pflugers Arch* 2017; 469(3–4): 419–430.
- Fransen M, Lismont C. Redox signaling from and to peroxisomes: Progress, challenges and prospects. *Antioxid Redox Signal*. 2018 February 13. doi: 10.1089/ars.2018.7515.
- Thomas DC. The phagocyte respiratory burst: Historical perspectives and recent advances. *Immunol Lett* 2017;192:88–96.
- Sies H, Berndt C, Jones DP. Oxidative Stress. *Annu Rev Biochem* 2017; 86: 715–748.
- Tanaka LY, Laurindo FRM. Vascular remodeling: A redox-modulated mechanism of vessel caliber regulation. *Free Radic Biol Med* 2017; 109: 11–21.
- Xu Q, Huff LP, Fujii M, Griendling KK. Redox regulation of the actin cytoskeleton and its role in the vascular system. *Free Radic Biol Med* 2017; 109: 84–107.
- Winterbourn CC. Biological production, detection, and fate of hydrogen peroxide. *Antioxid Redox Signal* 2017 December 14. doi: 10.1089/ars.2017.7425.
- Egea J, Fabregat I, Frapart YM et al. European contribution to the study of ROS: A summary of the findings and prospects for the future from the COST action BM1203 (EU-ROS). *Redox Biol* 2017; 13: 94–162.
- Montezano AC, Tsiropoulou S, Dulak-Lis M et al. Redox signaling, Nox5 and vascular remodeling in hypertension. *Curr Opin Nephrol Hypertens* 2015; 24(5): 425–433.

22. Park SW, Noh HJ, Sung DJ et al. Hydrogen peroxide induces vasorelaxation by enhancing 4-aminopyridine-sensitive Kv currents through S-glutathionylation. *Pflugers Arch* 2015; 467(2): 285–297.
23. Friederich-Persson M, Nguyen Dinh Cat A, Persson P et al. Brown adipose tissue regulates small artery function through NADPH Oxidase 4-derived hydrogen peroxide and redox-sensitive protein kinase G-1 $\alpha$ . *Arterioscler Thromb Vasc Biol* 2017; 37(3): 455–465.
24. Cifuentes-Pagano E, Meijles DN, Pagano PJ. The quest for selective nox inhibitors and therapeutics: Challenges, triumphs and pitfalls. *Antioxid Redox Signal* 2014; 20(17): 2741–2754.
25. Gray SP, Jandeleit-Dahm KA. The role of NADPH oxidase in vascular disease—hypertension, atherosclerosis & stroke. *Curr Pharm Des* 2015; 21(41): 5933–5944.
26. Holterman CE, Read NC, Kennedy CR. Nox and renal disease. *Clin Sci (Lond)* 2015; 128(8): 465–481.
27. Cheng G, Cao Z, Xu X et al. Homologs of gp91phox: Cloning and tissue expression of Nox3, Nox4, and Nox5. *Gene* 2001; 269(1–2): 131–140.
28. Montezano AC, Touyz RM. Reactive oxygen species, vascular Noxs, and hypertension: Focus on translational and clinical research. *Antioxid Redox Signal*. 2014; 20(1): 164–182.
29. Montezano AC, Touyz RM. Oxidative stress, Noxs, and hypertension: Experimental evidence and clinical controversies. *Ann Med* 2012;44(Suppl 1):S2–16.
30. Zhang M, Mongue-Din H, Martin D et al. Both cardiomyocyte and endothelial cell Nox4 mediate protection against hemodynamic overload-induced remodelling. *Cardiovasc Res* 2018; 114(3): 401–408.
31. Matsushima S, Kuroda J, Ago T et al. Increased oxidative stress in the nucleus caused by Nox4 mediates oxidation of HDAC4 and cardiac hypertrophy. *Circ Res* 2013; 112(4): 651–663.
32. Gray SP, Jha JC, Kennedy K et al. Combined NOX1/4 inhibition with GKT137831 in mice provides dose-dependent reno- and atheroprotection even in established micro- and macrovascular disease. *Diabetologia* 2017; 60(5): 927–937.
33. Di Marco E, Gray SP, Chew P et al. Differential effects of NOX4 and NOX1 on immune cell-mediated inflammation in the aortic sinus of diabetic ApoE $^{-/-}$  mice. *Clin Sci (Lond)* 2016; 130(15): 1363–1374.
34. Rivera J, Sobey CG, Walduck AK, Drummond GR. Nox isoforms in vascular pathophysiology: Insights from transgenic and knock-out mouse models. *Redox Rep* 2010; 15(2): 50–63.
35. Cowley AW Jr, Yang C, Zhelezova NN et al. Evidence of the importance of Nox4 in production of hypertension in dahl salt-sensitive rats. *Hypertension* 2016; 67(2): 440–450.
36. He L, He T, Farrar S et al. Antioxidants maintain cellular redox homeostasis by elimination of reactive oxygen species. *Cell Physiol Biochem* 2017; 44(2): 532–553.
37. Silva-Palacios A, Königsberg M, Zazueta C. Nrf2 signaling and redox homeostasis in the aging heart: A potential target to prevent cardiovascular diseases? *Ageing Res Rev* 2016; 26: 81–95.
38. Lopes RA, Neves KB, Tostes RC et al. Downregulation of nuclear factor erythroid 2-related factor and associated antioxidant genes contributes to redox-sensitive vascular dysfunction in hypertension. *Hypertension* 2015; 66(6): 1240–1250.
39. Gómez-Guzmán M, Jiménez R, Sánchez M et al. Epicatechin lowers blood pressure, restores endothelial function, and decreases oxidative stress and endothelin-1 and NADPH oxidase activity in DOCA-salt hypertension. *Free Radic Biol Med* 2012; 52(1): 70–79.
40. Kolisek M, Montezano AC, Sponder G et al. PARK7/DJ-1 dysregulation by oxidative stress leads to magnesium deficiency: Implications in degenerative and chronic diseases. *Clin Sci (Lond)* 2015; 129(12): 1143–1150.
41. Yamawaki H. A novel regulatory mechanism for differentiation of mesenchymal stem cell: Redox state of DJ-1 matters. *Proteomics* 2018 January; 18(1). doi: 10.1002/pmic.201700345.
42. Gao W, Shao R, Zhang X et al. Up-regulation of caveolin-1 by DJ-1 attenuates rat pulmonary arterial hypertension by inhibiting TGF $\beta$ /Smad signaling pathway. *Exp Cell Res* 2017; 361(1): 192–198.
43. Cuevas S, Zhang Y, Yang Y et al. Role of renal DJ-1 in the pathogenesis of hypertension associated with increased reactive oxygen species production. *Hypertension* 2012; 59(2): 446–452.
44. Montezano AC, Dulak-Lis M, Tsiropoulou S et al. Oxidative stress and human hypertension: Vascular mechanisms, biomarkers, and novel therapies. *Can J Cardiol* 2015; 31(5): 631–641.
45. Schiffrin EL. Antioxidants in hypertension and cardiovascular disease. *Mol Interv* 2010; 10(6): 354–362.
46. Mihalj M, Tadzic R, Vcev A et al. Blood pressure reduction is associated with the changes in oxidative stress and endothelial activation in hypertension, regardless of antihypertensive therapy. *Kidney Blood Press Res* 2016; 41(6): 721–735.
47. Wannamethee SG, Bruckdorfer KR, Shaper AG et al. Plasma vitamin C, but not vitamin E, is associated with reduced risk of heart failure in older men. *Circ Heart Fail* 2013; 6(4): 647–654.
48. Yamane T, Murao S, Kozuka M et al. Serum DJ-1 level is positively associated with improvements in some aspects of metabolic syndrome in Japanese women through lifestyle intervention. *Nutr Res* 2014; 34(10): 851–855.
49. Ge B, Song Y, Zhang Y et al. Glutathione S-transferase M1 (GSTM1) and T1 (GSTT1) null polymorphisms and the risk of hypertension: A meta-analysis. *PLOS ONE* 2015; 10(3): e0118897.
50. Kraja AT, Cook JP, Warren HR et al. New blood pressure-associated loci identified in meta-analyses of 475,000 individuals. *Circ Cardiovasc Genet* 2017; 10(5): pii: e001778.
51. De Ciuceis C, Amiri F, Brassard P et al. Reduced vascular remodeling, endothelial dysfunction, and oxidative stress in resistance arteries of angiotensin II-infused macrophage colony-stimulating factor-deficient mice: Evidence for a role in inflammation in angiotensin-induced vascular injury. *Arterioscler Thromb Vasc Biol* 2005; 25(10): 2106–2113.
52. Norlander AE, Madhur MS, Harrison DG. The immunology of hypertension. *J Exp Med* 2018; 215(1): 21–33.
53. Sun XN, Li C, Liu Y et al. T-cell mineralocorticoid receptor controls blood pressure by regulating interferon-gamma. *Circ Res* 2017; 120(10): 1584–1597.
54. Saleh MA, Norlander AE, Madhur MS. 2016. Inhibition of interleukin 17-A but not interleukin-17F signaling lowers blood pressure and reduces end-organ inflammation in angiotensin II-induced hypertension. *JACC Basic Transl Sci* 2016; 1: 606–616.
55. Chan CT, Sobey CG, Lieu M et al. Obligatory role for B cells in the development of angiotensin II-dependent hypertension. *Hypertension* 2015; 66(5): 1023–1033.
56. Wade B, Petrova G, Mattson DL. Role of immune factors in angiotensin II-induced hypertension and renal damage in Dahl salt-sensitive rats. *Am J Physiol Regul Integr Comp Physiol* 2018; 314(3): R323–R333.
57. Breitling S, Hui Z, Zabini D et al. The mast cell-B cell axis in lung vascular remodeling and pulmonary hypertension. *Am J Physiol Lung Cell Mol Physiol* 2017; 312(5): L710–L721.
58. Taleb S, Tedgui A, Mallat Z. Regulatory T-cell immunity and its relevance to atherosclerosis. *J Intern Med* 2008; 263: 489–499.
59. Schiffrin EL. Immune mechanisms in hypertension and vascular injury. *Clin Sci (Lond)* 2014; 126: 267–274.
60. Harrison DG, Guzik TJ, Lob HE et al. Inflammation, immunity, and hypertension. *Hypertension*. 2011; 57(2): 132–140.
61. Schiffrin EL. T lymphocytes: A role in hypertension? *Curr Opin Nephrol Hypertens* 2010; 19: 181–186.
62. Guzik TJ, Skiba DS, Touyz RM, Harrison DG. The role of infiltrating immune cells in dysfunctional adipose tissue. *Cardiovasc Res* 2017; 113(9): 1009–1023.
63. Viel EC, Lemarié CA, Benkirane K et al. Immune regulation and vascular inflammation in genetic hypertension. *Am J Physiol Heart Circ Physiol* 2010; 298(3): H938–H944.
64. Barhoumi T, Kasal DA, Li MW et al. T regulatory lymphocytes prevent angiotensin II-induced hypertension and vascular injury. *Hypertension* 2011; 57: 469–476.
65. Guzik TJ, Hoch NE, Brown KA et al. Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. *J Exp Med* 2007; 204: 2449–2460.
66. De Ciuceis C, Rossini C, Airò P et al. Relationship between different subpopulations of circulating CD4 $^{+}$  T-lymphocytes and microvascular structural alterations in humans. *Am J Hypertens* 2017; 30: 51–60.
67. De Ciuceis C, Agabiti-Rosei C, Rossini C et al. Relationship between different subpopulations of circulating CD4 $^{+}$  T lymphocytes and microvascular or systemic oxidative stress in humans. *Blood Press* 2017; 26: 237–245.
68. Kassan M, Wecker A, Kadowitz P et al. CD4 $^{+}$ CD25 $^{+}$ Foxp3 regulatory T cells and vascular dysfunction in hypertension. *J Hypertens* 2013; 31: 1939–1943.
69. Kassan M, Galan M, Partyka M et al. Interleukin-10 released by CD4 $^{+}$ CD25 $^{+}$  natural regulatory T cells improves microvascular endothelial function through inhibition of NADPH oxidase activity in hypertensive mice. *Arterioscler Thromb Vasc Biol* 2011; 11: 2534–2542.
70. Schiffrin EL. Immune mechanisms in hypertension: How do T-regulatory lymphocytes fit in? *J Hypertens* 2013; 31: 1944–1945.
71. Zhang J, Crowley SD. Role of T lymphocytes in hypertension. *Curr Opin Pharmacol* 2015; 21: 14–19.

72. Youn JC, Yu HT, Lim BJ et al. Immunosenescent CD8<sup>+</sup>T cells and C-X-C chemokine receptor type 3 chemokines are increased in human hypertension. *Hypertension*. 2013; 62: 126–133.
73. Itani HA, McMaster WG Jr, Saleh MA et al. Activation of human T cells in hypertension: Studies of humanized mice and hypertensive humans. *Hypertension* 2016; 68: 123–132.
74. Duftner C, Seiler R, Klein-Weigel P et al. High prevalence of circulating CD4<sup>+</sup>CD28<sup>-</sup> T-cells in patients with small abdominal aortic aneurysms. *Arterioscler Thromb Vasc Biol* 2005; 25: 1347–1352.
75. Gerli R, Schillaci G, Giordano A et al. CD4<sup>+</sup>CD28<sup>-</sup> T lymphocytes contribute to early atherosclerotic damage in rheumatoid arthritis patients. *Circulation* 2004; 109: 2744–2748.
76. Schiffrin EL. Immune modulation of resistance artery remodeling. *Basic Clin Pharmacol Toxicol* 2012; 110: 70–72.
77. Hansson GK, Libby P, Schonbeck U, Yan ZQ. Innate and adaptive immunity in the pathogenesis of atherosclerosis. *Circ Res* 2002; 91: 281–291.
78. Shao J, Nangaku M, Miyata T et al. Imbalance of T-cell subsets in angiotensin II-infused hypertensive rats with kidney injury. *Hypertension*. 2003; 42: 31–38.
79. Cheng X, Yu X, Ding YJ et al. The Th17/Treg imbalance in patients with acute coronary syndrome. *Clin Immunol* 2008; 127: 89–97.
80. Wang Q, Zhai X, Chen X et al. Dysregulation of circulating CD4<sup>+</sup>CXCR5<sup>+</sup> T cells in type 2 diabetes mellitus. *APMIS* 2015; 123: 146–151.
81. Caillon A, Mian MOR, Fraulob-Aquino JC et al.  $\gamma\delta$  T cells mediate angiotensin II-induced hypertension and vascular injury. *Circulation* 2017; 135: 2155–2162.
82. Scarsi M, Zanotti C, Chiarini M et al. Reduction of peripheral blood T cells producing IFN- $\gamma$  and IL-17 after therapy with abatacept for rheumatoid arthritis. *Clin Exp Rheumatol* 2014; 32: 204–210.
83. Ridker PM, Everett BM, Thuren T et al. Anti-inflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017; 377(12): 1119–1131.
84. Montaniel KR, Harrison DG. Is hypertension a bone marrow disease? *Circulation* 2016; 134: 1369–1372.
85. Lopez Gelston CA, Mitchell BM. Recent advances in immunity and hypertension. *Am J Hypertens* 2017; 30: 643–652.
86. Griendling KK, Touyz RM, Zweier JL et al. Measurement of reactive oxygen species, reactive nitrogen species, and redox-dependent signaling in the cardiovascular system: A scientific statement from the American Heart Association. *Circ Res* 2016; 119: e39–e75.
87. Savoia C. Immune cells in cardiovascular disease: Has the time arrived for new targets in human hypertension? *Am J Hypertens* 2017; 30:21–23.



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## INTRODUCTION

Sodium and potassium are the main extracellular and intracellular electrolytes, respectively, and are highly relevant to human nutrition: their dietary intakes have been associated with opposite effects on cardiovascular health.

This chapter reviews the evidence in favor of biological associations of both sodium and potassium intake with cardiovascular risk, addressing the possible mechanisms whereby sodium contributes to while potassium may protect from the development of cardiovascular disease (CVD) through their effects on blood pressure (BP) and possibly beyond.

## SODIUM

Sodium is an essential nutrient involved in the maintenance of normal cellular homeostasis and in the regulation of electrolyte balance and BP. Sodium balance is finely maintained by the kidneys, where angiotensin II, norepinephrine, aldosterone and insulin stimulate sodium and water reabsorption, whereas dopamine, cyclic AMP, the cardiac natriuretic peptides and prostaglandins exert a natriuretic effect. The amount of sodium in natural foods is quite modest and it has been the growing use of salt (sodium chloride 1 g = 17.1 mmol of sodium) for food preservation that has led to a progressive increase in its consumption in the most recent evolution of mankind (1). This excess is a recognized causative factor of hypertension and CVD; moreover, it contributes to the development of organ damage, such as renal dysfunction (2) and arterial stiffness (AS) (3).

## SODIUM INTAKE, BLOOD PRESSURE AND ORGAN DAMAGE

A number of experimental, epidemiological and intervention studies have established a causal role of sodium intake on BP increase with age and incidence of hypertension. The first epidemiological evidence was provided by the results of the INTERSALT study, showing that the higher the habitual sodium intake, the higher the average BP increase

with age and the prevalence of hypertension in different populations around the world (4). Many epidemiological surveys have been carried out to explore the relationship between sodium intake and BP, the most recent being the NHANES-2014 examination that confirmed a strong direct relationship between sodium intake (based on 24-h urine collection), BP and prevalence of hypertension (5).

The association between sodium intake and BP was strongly supported by the results of a carefully conducted experimental study in chimpanzees that, when switched from the habitual low-salt to a high-salt diet for 5 months, experienced a substantial increment of BP which later reverted to normal upon return to the usual low-salt regimen (6). In the Dietary Approaches to Stop Hypertension (DASH) sodium trial, a reduction in the sodium intake typical of the current American diet significantly reduced BP in hypertensive patients more than other dietary modifications, with no clinically apparent adverse effect (7). Several controlled clinical trials of the effect of dietary sodium reduction on BP were carried out and were the subjects of different meta-analyses. A comprehensive recent meta-analysis has reviewed 34 trials of at least 4 weeks' duration, involving a total of 3230 male and female participants (8). The meta-analysis showed an overall significant reduction in systolic BP of 4.2 mmHg and diastolic BP of 2.1 mmHg upon a mean sodium reduction of 75 mmol per day (4.4 g of salt). This significant trend was observed both in hypertensive patients (systolic BP: -5.4 mmHg, diastolic BP: -2.8 mmHg) and normotensive individuals (systolic BP: -2.4 mmHg; diastolic BP: -1.0 mmHg). In addition, the results of this meta-analysis indicated that salt reduction was associated with a small physiological increase in plasma renin activity, aldosterone, and noradrenaline and no significant change in lipid concentrations.

Noteworthy, a similar trend had been found by a previous meta-analysis investigating the effect of sodium reduction of at least 2 weeks' duration on BP in children and adolescents: in ten studies involving overall 966 children and adolescent participants, a reduction in sodium consumption of 42% led to a statistical significant BP fall of 1.2 and 1.3 mmHg for systolic and diastolic BP, respectively (9).

In addition to its effects on BP, several experimental studies suggested that elevated sodium intake promotes target-organ damage by different mechanisms (10–12). Studies on animal models showed that a high-salt diet may affect

arterial structure and function even without an increase in BP, by inducing the endothelial production of transforming growth factor-beta 1 (TGF- $\beta$ 1) and by decreasing the expression of endothelial nitric oxide synthase. Moreover, sodium overload was found to decrease the endothelial glycocalyx sodium barrier and to increase endothelial stiffness. Other studies pointed to the local renin–angiotensin–aldosterone system (RAAS) (heart, vessels and kidney) as one of the mediators of organ damage. Indeed, in animal experimental studies, a high-sodium regimen was shown to increase the expression of angiotensin II type 1 receptors (AT1-R) in the cardiovascular system and to increase the AT1-R density in the renal cortex while increasing the activity of the local RAAS. In keeping with these findings, the administration of an AT1-R blocker during sodium loading decreased aortic collagen accumulation and improved the cardiac, vascular and renal function. In addition, high sodium intake was reported to increase the levels of vascular and renal angiotensin-converting enzyme.

Dietary sodium intake may also affect the sympathetic nervous system (SNS) activity by increasing plasma osmolality, which is in turn associated with significant increments in plasma norepinephrine and muscle sympathetic nerve activity, additionally to the rise in BP.

Further to the experimental data, recent clinical studies also support a contribution of excess sodium intake to target-organ damage, even independently of increases in BP. Assessment of the effect of sodium intake on AS, an independent cardiovascular risk factor and a predictor of all-cause mortality (13), was the object of a recent meta-analysis, including 11 randomized controlled trials and 431 participants (3). The main results of this study indicated a statistically significant effect of reduction in sodium intake on AS (expressed as carotid-femoral pulse wave velocity). In particular, an average weighed difference of 89.3 mmol of sodium per day (5.2 g of salt) led to a 2.8% decrease in AS, at least in part independent of the changes in BP. The results were strengthened by the absence of significant heterogeneity among the studies, the lack of detectable publication bias, and the observation of a trend to AS decrease with salt restriction in the majority of the cohorts included.

In addition, urinary albumin excretion, an expression of subclinical organ damage and risk factor for the development and progression of renal disease (13), is associated with sodium intake. A meta-analysis of 23 studies (of which 11 were randomized controlled trials), including 516 male and female participants overall, indicated that sodium intake reduction markedly reduces albumin excretion (2). An average reduction in sodium intake of 92 mmol per day (5.4 g of salt) was significantly associated with a 32% reduction in urinary albumin excretion. The effect of sodium restriction was higher in the cohorts including patients on concomitant RAAS-blocking therapy in the studies with intervention lasting at least 2 weeks, and among participants with evidence of kidney damage.

Left ventricular hypertrophy, another expression of organ damage and independent predictor of cardiovascular morbidity and mortality (13), was positively associated with sodium intake in two studies apparently through the increase in BP (14,15). However, an intervention study showed that sodium restriction was associated with reduction in left ventricular mass, in part independently of BP decrease (16).

The so-called 'BP salt-sensitivity' may play a role in these results. The majority of individuals experience a decrease in BP when reducing dietary sodium intake. Actually, the

BP response to changes in salt intake exquisitely behaves as a continuous variable with a similar-Gaussian distribution (17), not allowing detection of any distinct subpopulation. Moreover, there is evidence that salt sensitivity of BP is associated with a higher incidence of hypertension and with other cardiometabolic risk factors. In addition to the genetic and demographic factors, several metabolic and neurohormonal conditions affect BP salt sensitivity, including excess body weight and its related alterations (such as insulin resistance, overactivity of the RAAS and of the SNS). Most of these conditions are in turn associated with altered renal sodium handling. These observations provide a plausible support for the strong unfavorable interaction observed in some studies between sodium intake and cardiovascular risk in individuals with excess body weight (18).

## SODIUM INTAKE AND CARDIOVASCULAR DISEASE

In consideration of the proven relationship between sodium intake and BP and of the additional BP-independent cardiovascular effects of high sodium intake, several longitudinal studies have investigated the impact of habitual sodium intake on the incidence of cardiovascular events.

The Scottish Heart Health Study, including 11,629 participants, found a significant association between sodium intake and risk of coronary heart disease in women and a positive but not significant trend in men (19). Another study performed in Finland showed that a 100 mmol higher urinary sodium excretion at baseline was associated with significantly higher coronary heart disease incidence, higher coronary heart disease death rate and higher mortality from all causes (20). In the Trials of Hypertension Prevention (TOHP) I (21) and TOHP II (22) intervention trials, including patients with pre-hypertension at baseline, a significant decrease in BP was achieved in the sodium-restricted group in comparison with the control group. Moreover, after 10–15 years of follow-up, a significantly lower risk of CVD was observed in the participants randomized to the sodium reduction group compared to controls, without further active intervention (23). A recent analysis of these cohorts confirmed the beneficial effect of low sodium intake and detected a significant linear association between sodium intake and mortality (24).

A strong direct association between sodium intake and stroke has also been detected in several longitudinal studies. The first meta-analysis of the available prospective studies carried out in samples of general population unequivocally showed a direct and significant association between higher sodium intake and risk of stroke (25). The analysis included the results of 13 studies published between 1998 and 2008, 170,000 participants and more than 11,000 vascular events. Based on a follow-up period of between 3.5 and 19 years, there was a 23% greater risk of stroke (and a 17% greater risk of total cardiovascular events) for an average difference in salt intake of 5 g of salt per day.

Further meta-analyses were later published. In one meta-analysis, the risk of stroke was calculated in 10 studies for a total of 72,878 individuals, again from general population samples (26). Higher compared with lower sodium intake was associated with a 24% higher rate of stroke, while a 32% greater risk of coronary heart disease mortality was achieved in a sample of 30,000 participants. A further meta-analysis by Graudal et al. pooled both studies on general population and studies in high cardiovascular risk individuals or

patients with clinical cardiovascular disorders (27). The comparison of high (more than 215 mmol/day) versus usual sodium intake (115–215 mmol/day) with seven studies and 186,091 individuals yielded a 21% higher rate of stroke in the first group, whereas the comparison of low (less than 115 mmol/day) sodium versus usual sodium, again with seven studies and 56,582 subjects, did not show a significant difference. This study, however, has been criticized because of inadequate assessment of sodium intake and of high risk of reverse causality due to the inclusion of cohorts of seriously ill patients under intensive medical treatment.

## SUMMARY AND RECOMMENDATIONS

A large amount of animal experimental investigation, epidemiological studies and controlled clinical trials support the causal relationship existing between excess sodium intake and cardiovascular health (26). In most countries worldwide the habitual average sodium intake largely exceeds the physiological needs and the recommended adequate intake determined on the basis of scientific evidence (28). Mainly on the basis that the majority of individuals experience a decrease in BP when reducing salt intake for a sufficiently prolonged period of time and that the decrease is linear upon reduction of salt intake to values below 5 g/day, a reduction of sodium chloride intake to 5 g (2 g of sodium) based on WHO recommendation (28,29) is recommended.

## POTASSIUM

The main sources of dietary potassium are vegetables, fruits and dairy products. In foods, potassium occurs as a mixture of organic and inorganic compounds, whereas potassium supplementation is most often provided as potassium-chloride (1 mmol of potassium = 39 mg). Several studies have detected an inverse relationship between dietary potassium intake and BP both within and across populations (30). In consideration of this association and because hypertension is the leading cause of CVD, it is conceivable to expect that potassium intake may affect cardiovascular morbidity and mortality.

## POTASSIUM INTAKE, BLOOD PRESSURE AND ORGAN DAMAGE

A relationship between dietary potassium intake and BP has long been known (4). A few studies evaluated the protective effect of a potassium-rich diet on the development of hypertension. The main findings of the Health Professionals Study were that the participants at potassium intake greater than 3.6 g/day had a reduced risk of hypertension of 35% than those on a lower intake (less than 2.4 g/day) (31). Likewise, in the Nurses' Health Study, baseline potassium intake greater than 3.2 g/day was related to a 23% lower risk of hypertension development in 4 years compared with an intake lower than 2 g/day (32). A more recent evaluation of the NHANES-2014 cohort, based on 24-h urine collections, again showed a strong and inverse relationship between urinary potassium excretion, BP and risk of hypertension (5).

Several randomized controlled trials of the effect of potassium supplementation on BP were carried out and their results have been examined in aggregate in several meta-analyses. The first such meta-analysis detected a significant reduction of 4.4 mmHg systolic and 2.5 mmHg diastolic BP in hypertensive patients upon increasing potassium intake by at least 0.78 grams per day (33). A smaller effect was observed in trials with normotensive individuals (systolic BP: –1.8 mmHg and diastolic BP: –1.0 mmHg). The antihypertensive effect of potassium supplementation was more pronounced in the presence of elevated sodium intake and in black participants compared with white. Similar results were provided by two more recent meta-analyses: one, including 22 trials with assessment of potassium intake by 24-h urinary potassium excretion, showed an overall BP reduction of 3.5/2.0 mmHg, with a greater effect in hypertensive subjects, in those who achieved a higher potassium intake and in those with a higher sodium intake (30). A third meta-analysis, including 25 trials of hypertensive participants, found that long-term supplementation with potassium salts reduced BP (systolic BP: 4.5 mmHg and diastolic BP: 3.0 mmHg), and that the effect was greater in individuals on antihypertensive treatment, having a high sodium intake and with baseline potassium intake less than 3.5 g per day (34).

As there might be a difference in the response to potassium supplementation provided (usually as potassium chloride) as a pharmacological preparation and one following a high potassium intake through natural foods in which potassium occurs as a combination of organic and inorganic compounds, it is important that some studies analyzed the effect of potassium-rich food consumption as an alternative to oral potassium supplements. A long-term randomized controlled trial evaluated the effects of increased potassium intake by an increase in fruit, vegetable and pulses consumption. After a 1-year follow-up, the participants assigned to the potassium-rich diet achieved and maintained a satisfactory BP control with less than half the amount of drugs needed by the control group (35).

The protective role of dietary potassium toward CVD may, however, include both the effects on BP regulation and other BP-independent effects. Indeed, many studies in animal models suggested that a high potassium intake may reduce cardiovascular organ damage and counteract the increase in cardiovascular event rates caused by a high sodium intake, even independently from its effect on BP (36).

A study on stroke-prone spontaneously hypertensive rats (SHR-SP) kept on a high sodium diet showed that a high versus low potassium intake was associated with a significant reduction in death rate. This antagonistic effect of potassium in relation to sodium was also shown in Dahl salt-sensitive rats, in which increased potassium intake neutralized sodium-induced renal damage and the release of endothelium- and macrophage-derived growth factors. Moreover, after exposure to a high potassium intake, significant decreases of lipid peroxide accumulation, endothelial permeability and macrophage adherence to the vascular wall were seen in the aortic wall and in the plasma of SHR-SP. In addition, *in vitro* investigations support a cardiovascular protective effect of high potassium diet toward organ damage caused by a salt load, at least in part through suppression of the production of reactive oxygen species (ROS) and through inhibition of vascular smooth muscle cell proliferation. Finally, potassium

supplementation in SHR-SP was shown to provide neuroprotection by reducing the ischaemic cerebral infarct size, whereas in DOCA-salt rats a potassium-rich diet led to a reduction of cardiac and renal hypertrophy, independently of reduction in BP.

Unfortunately, only few data are available about the effect of potassium supplementation on cardiovascular organ damage in humans. A randomized controlled trial on 42 mild hypertensive patients found that both potassium chloride and potassium bicarbonate supplementation improved AS (assessed as carotid-femoral pulse wave velocity) and endothelial function (expressed as brachial artery flow-mediated dilatation), decreased left ventricular mass and ameliorated left ventricular diastolic function when compared with placebo (37). No difference between the two potassium salts was detected. On the other hand, only potassium chloride supplementation also reduced 24-h urinary albumin excretion.

The data on the effects of potassium supplementation on AS were pooled in a recent meta-analysis including a small number of randomized controlled trials (38). The main results confirmed the favourable trend; however, potassium supplementation significantly improved only pulse pressure, while a not significant reduction in pulse wave velocity and augmentation index was detected.

## POTASSIUM INTAKE AND CARDIOVASCULAR DISEASE

Given the clear-cut relationship between potassium intake and BP, and considering the additional and in part BP-independent cardiovascular effects of potassium supplementation, a number of studies over three decades have also explored the possible association between habitual dietary potassium intake and the incidence of cardiovascular events.

A particularly strong inverse association has been demonstrated between potassium intake and risk of stroke. A pioneer observational investigation including 859 men and women showed that a 10-mmol increase in daily consumption of potassium was associated with a 40% reduction in the risk of stroke mortality, after a 12-year follow-up observation (39). Other observational studies such as NHANES I, Health Professionals' Study and Nurses' Health Study also reported a similar favorable association. Accordingly, all the following systematic reviews and meta-analyses of cohort studies on samples of adult general population confirmed an inverse and significant association between habitual potassium intake and risk of stroke (30,40–44). In a comprehensive analysis, including 14 cohorts for a total of 333,250 people and more than 10,600 stroke events, an average weighted difference of 1.5 g per day between higher versus lower dietary potassium consumption was associated with a 20% lower risk of stroke (42). In dose-response analyses, an increase of 1.0 g per day in dietary K intake (approximately 25% of the adequate intake according to most international dietary guidelines) was linearly associated with a 10% (41) and 11% (42) reduction in stroke rates. The analysis of stroke subtypes confirmed a significant inverse association of dietary potassium intake with both ischaemic and haemorrhagic stroke (44).

Much less data are available concerning the effect of potassium supplementation and risk of cerebrovascular

events. A beneficial effect was suggested both for men (45) and women (43), but the effect was significant only for men (45).

A small number of studies are available on the effect of potassium consumption on occurrence of total cardiovascular events and coronary heart disease.

A meta-analysis of prospective studies in samples of general population showed an inverse and significant association between higher habitual potassium intake and risk of CVD (40). In particular, the analysis based on the results of six cohorts, including 82,000 people and more than 3000 coronary heart disease events, detected a 7% lower risk of coronary heart disease for 1.4 g per day difference in potassium intake. In addition, the analysis of total cardiovascular events based on four cohorts, 62,000 participants and 2500 events found a 26% lower risk of total cardiovascular events for an average difference of 1.3 g per day. The trend was substantially confirmed by a more recent meta-analysis that included only trials with assessment of potassium intake by 24-h urinary potassium excretion (30).

## SUMMARY AND RECOMMENDATIONS

In conclusion, experimental, clinical and epidemiological studies consistently support a favourable effect of dietary potassium intake on stroke risk and stroke mortality, at least in part independently of its well-recognized beneficial effect on BP. More data are needed to reach a firm conclusion about the relationship between potassium supplementation and cardiovascular events rate.

Based on the large body of evidence available, most national authorities recommend as adequate a potassium intake of 90 mmol or more per day (3.5 g per day) for the adult population, with the exception of individuals with renal disease compromising potassium handling (46).

## REFERENCES

1. Leclercq C, Ferro-Luzzi A. Total and domestic consumption of salt and their determinants in three regions of Italy. *Eur J Clin Nutr* 1991; 45: 151–159.
2. D'Elia L, Rossi G, Schiano di Cola M et al. Meta-analysis of the effect of dietary sodium restriction with or without concomitant renin-angiotensin-aldosterone system-inhibiting treatment on albuminuria. *Clin J Am Soc Nephrol* 2015; 10: 1542–1552.
3. D'Elia L, Galletti F, La Fata E et al. Effect of dietary sodium restriction on arterial stiffness: Systematic review and meta-analysis of the randomized controlled trials. *J Hypertens* 2018; 36(4): 734–743.
4. Intersalt Cooperative Research Group. Intersalt: An international study of electrolyte excretion and blood pressure. Results for 24-hour urinary sodium and potassium excretion. *BMJ* 1988; 297: 319–328.
5. Jackson SL, Cogswell ME, Zhao L et al. Association between urinary sodium and potassium excretion and blood pressure among adults in the United States: National Health and Nutrition Examination Survey, 2014. *Circulation* 2018; 137(3): 237–246.
6. Denton D, Weisinger R, Mundy NI et al. The effect of increased salt intake on blood pressure of chimpanzees. *Nat Med* 1995; 1: 1009–1016.
7. Svetkey LP, Sacks FM, Obarzanek E et al. The DASH Diet, Sodium Intake and Blood Pressure Trial (DASH-sodium): Rationale and design. DASH-Sodium Collaborative Research Group. *J Am Diet Assoc* 1999; 99(8 Suppl): S96–104.
8. He FJ, Li J, Macgregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomized trials. *BMJ* 2013; 346: f1325.



9. He FJ, Mac Gregor GA. Importance of salt in determining blood pressure in children: meta-analysis of controlled trials. *Hypertension* 2006; 48: 861–869.
10. Edwards DG, Farquhar WB. Vascular effects of dietary salt. *Curr Opin Nephrol Hypertens* 2015; 24(1): 8–13.
11. Frohlich ED. The salt conundrum: A hypothesis. *Hypertension* 2007; 50: 161–166.
12. Stocker SD, Monahan KD, Browning KN. Neurogenic and sympathoexcitatory actions of NaCl in hypertension. *Curr Hypertens Rep* 2013; 15: 538–546.
13. Mancia G, Fagard R, Narkiewicz K et al. Task Force Members: 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1281–1357.
14. Kupari M, Koskinen P, Virolainen J. Correlates of left ventricular mass in a population sample aged 36 to 37 years. Focus on life-style and salt intake. *Circulation* 1994; 89: 1041–1050.
15. Schmieder RE, Messerli FH, Garavaglia GE, Nunez BD. Dietary salt intake. A determinant of cardiac involvement in essential hypertension. *Circulation* 1988; 78: 951–956.
16. Jula AM, Karanko HM. Effects on left ventricular hypertrophy of long-term non-pharmacological treatment with sodium restriction in mild-to-moderate essential hypertension. *Circulation* 1994; 89: 1023–1031.
17. Weinberger MH, Miller JZ, Luft FC et al. Definitions and characteristics of sodium sensitivity and blood pressure resistance. *Hypertension* 1986; 8(pt 2): II127–II134.
18. He J, Ogden LG, Vupputuri S et al. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. *JAMA* 1999; 282: 2027–2034.
19. Tunstall-Pedoe H, Woodward M, Tavendale R et al. Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish Heart Health Study: Cohort study. *BMJ* 1997; 315: 722–729.
20. Tuomilehto J, Jousilahti P, Rastenyte D et al. Urinary sodium excretion and cardiovascular mortality in Finland: A prospective study. *Lancet* 2001; 357: 848–851.
21. TOHP I. The effects of non-pharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. *JAMA* 1992; 267: 1213–1220.
22. TOHP II. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, phase II. *Arch Intern Med* 1997; 157: 657–667.
23. Cook NR, Cutler JA, Obarzanek E et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: Observational follow-up of the Trials of Hypertension Prevention (TOHP). *BMJ* 2007; 334: 885–888.
24. Cook NR, Appel LJ, Whelton PK. Sodium intake and all-cause mortality over 20 years in the trials of hypertension prevention. *J Am Coll Cardiol* 2016; 11; 68(15): 1609–1617.
25. Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: Meta-analysis of prospective studies. *BMJ* 2009; 339: b4567.
26. Aburto NJ, Ziolkovska A, Hooper L et al. Effect of lower sodium intake on health: Systematic review and meta-analyses. *BMJ* 2013; 346: f1326.
27. Graudal N, Jürgens G, Baslund B, Alderman MH. Compared with usual sodium intake, low and excessive-sodium diets are associated with increased mortality: A meta-analysis. *Am J Hypertens* 2014; 27: 1129–1137.
28. World Health Organization. *Guideline: Sodium Intake for Adults and Children*. WHO Document Production Services, Geneva, Switzerland, 2012.
29. World Health Organization. *Global Action Plan for the Prevention and Control of Non-Communicable Diseases 2013–2020*. WHO Document Production Services, Geneva, Switzerland; 2013.
30. Aburto NJ, Hanson S, Gutierrez H et al. Effect of increased potassium intake on cardiovascular risk factors and disease: Systematic review and meta-analyses. *BMJ* 2013; 346: f1378.
31. Ascherio A, Rimm EB, Giovannucci EL et al. A prospective study of nutritional factors and hypertension among US men. *Circulation* 1992; 86: 1475–1484.
32. Witterman JCM, Willett WC, Stampfer MJ et al. A prospective study of nutritional factors and hypertension among US women. *Circulation* 1989; 80: 1320–1327.
33. Whelton PK, He J, Cutler JA et al. Effect of oral potassium on blood pressure meta-analysis of randomized controlled clinical trials. *JAMA* 1997; 277: 1624–1632.
34. Filippini T, Violi F, D'Amico R, Vinceti M. The effect of potassium supplementation on blood pressure in hypertensive subjects: A systematic review and meta-analysis. *Int J Cardiol* 2017; 230: 127–135.
35. Siani A, Strazzullo P, Giacco A et al. Increasing the dietary potassium intake reduces the need for antihypertensive medication. *Ann Intern Med* 1991; 115: 753–759.
36. Castro H, Raij L. Potassium in hypertension and cardiovascular disease. *Semin Nephrol* 2013; 33(3): 277–289.
37. He FJ, Marciniak M, Carney C et al. Effects of potassium chloride and potassium bicarbonate on endothelial function, cardiovascular risk factors, and bone turnover in mild hypertensives. *Hypertension* 2010; 55(3): 681–688.
38. Tang X, Wu B, Luo Y et al. Effect of potassium supplementation on vascular function: A meta-analysis of randomized controlled trials. *Int J Cardiol* 2017; 228: 225–232.
39. Khaw TK, Barrett-Connor E. Dietary potassium and stroke associated mortality. *N Engl J Med* 1987; 316: 235–240.
40. D'Elia L, Barba G, Cappuccio FP, Strazzullo P. Potassium intake, stroke, and cardiovascular disease. A meta-analysis of prospective studies. *J Am Coll Cardiol* 2011; 57: 1210–1219.
41. Larsson SC, Orsini N, Wolk A. Dietary potassium intake and risk of stroke: A dose-response meta-analysis of prospective studies. *Stroke* 2011; 42: 2746–2750.
42. D'Elia L, Iannotta C, Sabino P, Ippolito R. Potassium rich-diet and risk of stroke: Updated meta-analysis. *NMCD* 2014; 24: 585–587.
43. Adebamowo SN, Spiegelman D, Willett WC, Rexrode KM. Association between intakes of magnesium, potassium, and calcium and risk of stroke: 2 cohorts of US women and updated meta-analyses. *Am J Clin Nutr* 2015; 101(6): 1269–1277.
44. Vinceti M, Filippini T, Crippa A et al. Meta-analysis of potassium intake and the risk of stroke. *J Am Heart Assoc* 2016; 5: pii: e004210.
45. Adebamowo SN, Spiegelman D, Flint AJ et al. Intakes of magnesium, potassium, and calcium and the risk of stroke among men. *Int J Stroke* 2015; 10(7): 1093–1100.
46. World Health Organization. *Potassium intake for adults and children. Guideline*. World Health Organization (WHO), Geneva; 2012.



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# STRUCTURAL CARDIOVASCULAR CHANGES IN HYPERTENSION

# 10

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## INTRODUCTION

The basic structure of the cardiovascular system is determined early in the development of an individual. However, after birth, and even in adult stages of life, the structure of the heart and blood vessels are not static: these structures undergo constant remodelling. Remodelling can be part of an adaptive process in which the altered structure contributes to homeostatic control of, for instance, mechanical forces in the heart and blood vessels. Remodelling can also be part of a pathological series of events in the cardiovascular system and its end organs.

Hypertension is associated with both types of remodelling. In hypertensive individuals, structural changes in the heart and blood vessels have been observed even in the early phase of blood pressure elevation. In the long term, these structural alterations form a key factor in the maintenance of an elevated blood pressure. In this chapter, the major structural changes in the heart and blood vessels in hypertension are reviewed. Furthermore, this chapter discusses how these changes contribute to the target-organ damage in hypertensive disease.

## STRUCTURAL CHANGES IN THE HEART

Elevated blood pressure leads to the development of structural changes in the heart. These changes consist mainly in the presence of left ventricular hypertrophy (LVH), of increased collagen content in the myocardium and in coronary vascular alterations.

## PATHOGENESIS OF LVH IN HYPERTENSION

The development of LVH initially represents a mechanism of adaptation of the heart to the increased pressure load, in order to reduce the wall stress and to maintain a normal cardiac output and ejection fraction. High blood pressure represents the main determinant of the sequence of events which induce LVH. In fact, hypertension induces an increase of myocyte width which translates into an increase of cardiac wall thickness. The development of

hypertensive heart disease is characterized not only by myocyte hypertrophy, but also by apoptosis, fibrosis and structural changes in the wall of small and large coronary arteries. Concentric LVH (increase of cardiac mass without increase of chamber volume) is the consequence of predominant pressure load, while a predominant volume load is responsible for eccentric LVH (increase of cardiac mass and of chamber volume) (1).

In recent years, the sequence of events leading from increased myocardial wall stress to LVH has been intensively studied. In the signalling cascade there is a central role for intracellular calcium release, which is an early response to mechanical and humoral myocyte stretch factors, including angiotensin II and endothelin. The increase in intracellular calcium results in activation of calcineurin, which dephosphorylates transcription factors of genes that lead to myocyte hypertrophy, such as beta-myosin heavy chain and beta-skeletal actin (2,3).

These molecular genetic studies suggest that not only hemodynamic load, but also several neurohumoral factors may have an important role in the development of LVH. Nonhemodynamic factors that may have a role in the development and degree of LVH include age, gender, race, obesity, diabetes, renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system (SNS) inflammation, salt intake and large artery stiffness. In addition, several studies have suggested that approximately 30–60% of the left ventricular mass (LVM) variance may be due to genetic factors (4). Among candidate genes which may influence the development of LVH are genes related to the RAAS, the natriuretic peptide family, the SNS and/or its receptor–signalling cascade.

## CARDIAC STRUCTURAL CHANGES AND ALTERED FUNCTION IN HYPERTENSION

Cardiac organ damage in hypertension is traditionally identified by LVH, which is an independent predictor of cardiovascular morbidity and mortality, representing an increased risk for ischaemic heart disease, stroke and eventually congestive heart failure (HF). However, the geometric adaptation to the increased load is more complex, and it has been recently classified according to LVM, left

ventricle (LV) volume and relative wall thickness (RWT) or LVM/volume ratio. Using this approach, different patterns of geometric adaptation can be identified, i.e. non-dilated ventricles, concentric remodelling or concentric LVH, eccentric remodelling or eccentric LVH. Concentric hypertrophy is the condition associated with the highest cardiovascular risk. The assessment of LVH is performed using the classical electrocardiogram, the more sensitive echocardiographic technique (both two- and three-dimensional), and with cardiac magnetic resonance imaging, which is the gold standard, but often of limited availability, relatively costly and time consuming (5,6).

In early, mild hypertension, even before the detection of LVH, the first manifestation of cardiac organ damage may be LV diastolic dysfunction, usually clinically assessed by echo Doppler examination. This abnormality is even more evident with the development of LVH and increased collagen content in the LV, being often associated with enlargement of the left atrium, as a consequence of increased LV filling pressure. In addition, systolic function may be reduced, but usually a depressed LV pump function may be detected in an advanced stage of cardiac organ damage.

Most patients with longstanding hypertension, particularly those with LVH, ultimately develop HF, and therefore in about 70–75% of patients with HF a history of hypertension may be present (7,8). In fact, with sustained pressure overload, the development of LVH and the impairment of diastolic function lead to the clinical signs and symptoms of HF with preserved ejection fraction (HFpEF), which is above 50%. In this transition, fibrosis of the interstitium of the myocardium plays a central role. Fibrosis can be triggered by humoral factors. The RAAS is again a key factor in initiating fibrotic changes in the heart, in particular via the action of aldosterone (9). Other important mediators include matrix metalloproteinases (10), integrins such as osteopontin (11), and inflammatory cytokines, including transforming growth factor beta. Recent research has focused on the role of reactive oxygen species in the fibrotic changes of the heart and in cardiac remodelling (12,13). All these mediators are now important targets for novel drugs in the regression of LV structural changes.

Patients with HFpEF are usually older women with a long history of hypertension, frequently obese, with diabetes, hyperlipidaemia and atrial fibrillation. Hypertension may also favour the development of coronary artery disease and of an enlarged LV (eccentric LVH), with reduction of systolic function, as assessed by EF, leading to HF with reduced EF (HFrEF). Further studies are needed in order to clarify whether there is usually a transition from concentric LVH to HF with normal LV dimension to dilated HF, or whether HFpEF and HFrEF should be considered two separate entities, related to differences in hemodynamics, neurohumoral activation and/or genetic factors (1,8).

## STRUCTURAL CHANGES IN THE CORONARY VASCULAR BED

In hypertensive patients, coronary vascular resistance and coronary perfusion pressure are increased (14). The increase in coronary resistance has been reported in patients with LVH but also in those without LVH (15), thus suggesting an important role for coronary angiopathy independent of LVH. In any case, vascular structural changes are usually

more evident in patients with concentric LVH (16). Several mechanisms may be involved in the pathophysiology of coronary angiopathy (1,17,18). The first is endothelial dysfunction causing an impaired vasodilator potential of coronary microvessels. In addition, hypertension favours an increased atherosclerotic process leading to accelerated development of plaques in coronary epicardial arteries. A further mechanism is a structural inward remodelling of the coronary arterial wall, causing an increased wall/lumen ratio of small coronary arteries and arterioles. This remodelling can occur in combination with perivascular fibrosis and subsequent compression of the outer surface of these small vessels (19). Finally, reduction of the number of small arteries, arterioles and capillaries (rarefaction) is a further mechanism that induces reduced coronary perfusion (19–21).

Coronary reserve, a measure of the capacity of the coronary vasculature to respond maximally to vasodilator agents, is significantly decreased in hypertensive patients (18). Presumably, under conditions of increased myocardial oxygen demand, decreased ability to dilate the coronary microvasculature translates into diffuse ischemia and infarction. Such a propensity to ischemia may explain some of the increased risk for coronary events and sudden cardiac death, particularly in patients with LVH. In addition, impaired subendocardial blood flow may contribute to diastolic dysfunction and increase the risk and severity of HF. The microcirculation is more often abnormal in HFpEF (8). The role of the microcirculation is dealt with more fully in the section below concerned with the structure and function of resistance vessels.

## STRUCTURAL CHANGES IN BLOOD VESSELS

Hypertension is associated with a range of structural changes in the vasculature. The nature of the changes and their functional consequences differ per segment of the vascular tree (Table 10.1). The most significant alterations occur on the arterial side and in the microcirculation. With respect to arterial structural changes, a distinction can be made in large arteries (the aorta and its side branches), and resistance vessels. The large arteries primarily serve a conduit and compliance function, whereas the small arteries and arterioles control vascular resistance. The difference

**Table 10.1** Segments of the vascular tree and their structural change in hypertension

| Segment of the vascular tree | Structural change                       | Functional consequence |
|------------------------------|-----------------------------------------|------------------------|
| Large arteries               | Vascular smooth muscle cell hypertrophy | Distensibility ↓       |
|                              | Extracellular matrix composition        |                        |
| Resistance vessels           | Inward remodelling                      | Resistance ↑           |
|                              | Rarefaction                             |                        |
| Capillaries                  | Rarefaction                             | Tissue ischemia        |

between large and resistance arteries is also reflected in the heterogeneity of the way in which they remodel in response to a rise in BP. Large arteries adapt to increased pressure by expressing early response genes that lead to vascular smooth muscle cell (VSMC) hypertrophy and an increased wall thickness. Small arteries, on the other hand, rapidly constrict without changing wall material (eutrophic inward remodelling) and thereby normalizing wall stress. Only in severe hypertension, small vessels may also undergo hypertrophic remodelling (22).

The basic architecture of arteries is usually described in terms of cross-sectional arrangement of cells and extracellular matrix. Cells include the endothelial cell layer and VSMCs. The extracellular matrix consists of lamellae of elastic material with intervening layers of VSMCs, collagen fibres and ground substance (23). However, the distribution of elastin and collagen varies markedly along the longitudinal axis. In the proximal aorta, elastin is the dominant component, whereas in the distal aorta and its side branches, as well as in the smaller arteries, collagen predominates. The smaller the arteries become, the more VSMCs predominate. These differences find their origin in the early development of the vascular system. The reader is referred to the specialized literature for further details on this aspect of vascular development (23).

## LARGE ARTERY STRUCTURE AND FUNCTION IN HYPERTENSION

In hypertensive patients, the stiffness of large arteries is usually increased. Arterial stiffening is part of the ageing process, but it is accelerated in humans prone to develop hypertension (24). A complex interplay of molecular, cellular and functional modifications of the arterial wall contributes to the increased stiffness. The French school of vascular investigators who have made important contributions to this field of research have recently reviewed this complex interplay in detail (24,25). Epidemiological studies have shown that up to 40% of the variance in indices for arterial stiffness may be genetically determined (26). The major genetic factors that determine arterial stiffness have been reviewed (27,28). Furthermore, the relationship between polymorphisms of several candidate genes and arterial stiffness has been investigated. Various candidate genes of the RAAS play a key role in arterial stiffness. However, the contribution of a given polymorphism to the variance of a specific phenotype is limited (27,28). In subjects of the Flemish Study on Environment, Genes and Heat Outcomes (FLEMINGHO) we found a much stronger contribution in individuals showing specific combinations of gene variants (29). For instance, the combination of angiotensin-converting enzyme DD subjects homozygous for alpha-adducin gly 460 was a powerful predictor of increased large artery stiffness (29).

Another genetic approach, particularly followed by Lacolley, Laurent and their co-workers, is the study of large artery properties in subjects with monogenic disease or in knockout mice with phenotype changes in arterial wall properties (25,27). The data obtained following this approach highlight the role of vascular smooth muscle cells and extracellular matrix components. Furthermore, the data show that collagen and elastin are not simply passive compounds that can be elastic or rigid, but that they

are also involved in the control of VSMC function, such as migration, proliferation, adhesion and cytoskeletal rearrangement (25,27) and may thus influence large artery properties in different ways.

The molecular basis of arterial stiffness has been the topic of recent intensive research with a particular focus on vascular calcification (30) and histone metabolism (31). A recent study provides the transcriptomic landscape of human aortic VSMCs in response to extracellular matrix stiffness and identifies novel stiffness-sensitive human long noncoding RNAs (32). Nongenomic influences also contribute importantly to the increased large artery stiffness in hypertension. One factor is the elevated blood pressure as such. An elevated pressure shifts the pressure-distensibility relationship toward a lower distensibility value (33,34). This observation led to the conclusion that hypertension-induced large artery hypertrophy is not necessarily associated with increased arterial stiffness (33). Despite increased wall thickness due to VSMC hypertrophy, the stiffness of the artery wall material as assessed by the modules of elasticity is not increased in hypertensive patients or in the spontaneously hypertensive rat (33).

Another source of nongenomic influence on large artery structure and function is a range of humoral and metabolic products. It is beyond the scope of this contribution to discuss all these products in detail. The RAAS has received the most attention in this respect (35,36). Its major mediators – angiotensin II and aldosterone – affect arterial structure considerably and beyond their effects on BP. They activate signal transduction pathways that promote VSMC growth, inflammation and fibrosis. Studies in both experimental animals and humans with hypertension suggest that drugs blocking the RAAS have an impact on early mechanisms of vascular disease, such as endothelial dysfunction and arterial remodelling (36).

The clinical significance of arterial stiffness is considerable. Clinical studies have demonstrated that large artery stiffness is a strong risk factor and contributor to heart failure, coronary heart disease, stroke, cognitive impairment, chronic kidney disease and aneurysms (24,37). The pathophysiological basis of this enhanced risk for target-organ damage—related diseases is the abnormal pulsatile hemodynamics due to arterial stiffening that causes microvascular dysfunction (38). In particular, large artery stiffening produces impedance matching that reduces wave reflection and exposes the microcirculation to excessive pulsatile stress, resulting in microvascular target-organ damage and dysfunction. The reader is referred to recent detailed reviews on this topic (38,39).

## STRUCTURE AND FUNCTION OF RESISTANCE ARTERIES IN HYPERTENSION

The precapillary vessels distal to the large (conduit) arteries are collectively known as resistance vessels. These vessels consist of the arterioles (vessels with only one layer of smooth muscle cells) and the more proximal small arteries. The division between large and small arteries is arbitrarily set to vessels with diameter ca. 200  $\mu\text{m}$  (40), keeping in mind that there is considerable cross-talk between the

large arteries and the resistance vessels (41,42). The resistance vessels contribute to the major part of the peripheral resistance and to its control. Furthermore, the resistance vessels are responsible for the increased peripheral resistance seen in established essential hypertension, and the resistance vessels thus play a key role in the pathogenesis of this disease.

In principle, the increased resistance of the resistance vessels can be due either to a narrowing of the lumen or to a rarefaction (with fewer parallel-connected vessels). Evidence concerning narrowing of the vessels has been obtained primarily from gluteal biopsies of small arteries (43), findings that have been widely confirmed (44). Evidence for rarefaction in essential hypertension is older (45) but again has been widely confirmed (21,46). The clinical relevance of microvascular structure as a prognostically relevant endpoint has been recently reviewed (47).

## HEMODYNAMIC STUDIES

Measurements of peripheral resistance using forearm plethysmography as pioneered by Folkow (48) have repeatedly indicated a structural basis for increased resistance of the resistance vasculature in essential hypertension. Such hemodynamic studies have been extended to other vascular beds, including the coronary circulation where essential hypertension has been shown to be associated with a reduced coronary reserve (49). Such studies have also shown that in essential hypertension, compared to controls, excessive microvascular structural abnormalities in the coronary and peripheral circulations are raised proportionally more than the blood pressure, suggesting that structural changes might precede the rise in blood pressure (50). An alternative approach is based on analysis of the pulse wave, where reflection of the pulse from the resistance vasculature causes an increase in the augmentation index (AIx) (51). To some extent the AIx is a measure of the resistance vessel structure (52), and recent evidence has indicated that AIx is increased in offspring of essential hypertensive parents independent of blood pressure (53).

## EX VIVO EVIDENCE

The reason for the narrowing of resistance vessels in hypertension appears to be primarily due to changes in structure, and few functional changes have been observed (54). The structural change is an inward eutrophic remodelling: a reorganization of the VSMC around a narrower lumen (55,56). Indeed, Schiffrin and co-workers (57) concluded from their observations that small artery structure is one of the first manifestations of target-organ damage, occurring before proteinuria or cardiac hypertrophy. In addition to these changes in VSMC structure and function, the extracellular matrix is critically important in the altered properties of small arteries in hypertensive subjects. With chronic vasoconstriction, some degree of cell migration, secretion of fibrillar and nonfibrillar components, and rearrangement of extracellular matrix-cell interactions may occur (44). Data from gluteal subcutaneous small arteries have indicated an age-dependent increase in reactive oxygen species (ROS) and in collagen in both essential hypertension (EH) and normotension (NT), greatest in EH (56–58).

In renovascular hypertension, patients exhibit hypertrophic remodelling of small arteries due to smooth muscle cell hypertrophy, without evidence of hyperplasia (59).

The prognostic value of abnormal small artery structure has been investigated in a number of studies. These studies have shown that an increased media-to-lumen ratio of gluteal small arteries is associated with increased cardiovascular risk (60,61). There is also evidence that a hypertrophic response of the more proximal small arteries to essential hypertension is predictive of additional cardiovascular risk (62).

Izzard et al. (62) have reviewed the mechanisms of inward eutrophic remodelling of small arteries from essential hypertensive individuals. Their conclusion was that chronic vasoconstriction is the stimulus for a structural reduction in lumen diameter, a conclusion supported by more recent experimental studies (63). The nature of the contractile stimulus is still not fully resolved. Neural or humoral factors may be involved, although Izzard et al. (62) favour the myogenic properties of the small arteries as the underlying mechanism. The myogenic vasoconstriction could serve to maintain wall stress at constant value. Patients with type 2 diabetes show a severely impaired myogenic constriction to increases in intraluminal pressure. In these patients, impaired myogenic tone would increase wall stress and thereby promote small artery hypertrophy (62). The molecular pathways may include tissue transglutaminase (64,65) and ROS-activated MMP9 (66). Schiffrin and co-workers (67) have recently obtained evidence that low-grade inflammation plays an important role in small artery remodelling. In particular, activated T cells may contribute to vascular remodelling directly on blood vessels via effects of the cytokines produced or indirectly by actions on the kidney (67). Similar evidence for a role of angiotensin II type-1 receptor-mediated immune responses in the development of vascular changes in hypertension has been found (68).

## DIRECT OBSERVATION

The possibility that the increased peripheral resistance in essential hypertension is associated with rarefaction of the arterioles was supported by numerous animal studies where selected vascular beds could be examined either in vivo or histologically (69,70). Microvascular rarefaction has two major consequences. Firstly, reduction of arteriolar density increases vascular resistance. Secondly, it disturbs the tissue delivery of oxygen and nutrients, thus contributing to target-organ damage in hypertension. Microvascular rarefaction can be functional or structural. Functional rarefaction refers to an abnormally low prevalence of anatomically existing but nonperfused microvessels. Structural rarefaction represents a situation in which the microvessels are anatomically absent. This can be due either to active elimination of microvessels or to a lack of growth during the development of microvascular networks (71). In humans, Ruedemann in 1933 reported that hypertensive patients had an abnormally low number of small conjunctival vessels (45). The relevance of rarefaction for human essential hypertension has been demonstrated in the skin vasculature (46,72). There is also evidence that rarefaction precedes the onset of hypertension (73) suggesting that the primary defect in angiogenic mechanisms could be responsible for the development of hypertension.



The cause-and-effect relationships between microvascular rarefaction and hypertension are still under discussion. Various authors have shown that mechanical forces due to increased pressure and/or flow may cause structural arteriolar and capillary rarefaction (70). Conversely, antiangiogenic treatment of cancer can cause hypertension (74,75). Rarefaction has been proposed linked to a lack of bone marrow–derived endothelial progenitor cells (EPC) (76). However, the role of EPCs is complex (77) and a clear relationship of EPCs to hypertension has not been established.

The retinal microcirculation has long been known to be abnormal in hypertension (78,79) and an important tissue to study for hypertension-related organ damage (80). Retinal microcirculatory imaging techniques have substantial reproducibility (81,82) and can be used repeatedly in the same individuals for follow-up. Retinal microcirculatory analysis has been used for the risk stratification of hypertensive patients since it shows a strong association with the risk to develop stroke (79), coronary heart disease (83) and renal complications (84).

More recently, a major advance in the ability to analyze the retinal microcirculation was developed using scanning-laser Doppler flowmetry (SLDF) (85). This technique is able to measure lumen diameter and wall thickness of selected resistance vessels, and also to measure rarefaction (86). The technique has been validated indirectly (87). Using this technique, increased wall-to-lumen ratio has been demonstrated in patients with hypertension (85). A similar technique has been used to confirm these findings in a large study (88) where wall-to-lumen ratio correlated with blood pressure independent of age (89). In a small study, Raff and colleagues (90) showed that increased salt intake in treatment-resistant EHs caused increased wall-to-lumen ratio and hypertrophy of retinal small arteries using SLDF. However, although these techniques are a potentially powerful approach to risk assessment of patients with essential hypertension, the technique is not readily available, and no long-term prognostic studies have yet been performed (47).

## TREATMENT

Ex vivo analysis of gluteal small arteries from EHs before and after a period of antihypertensive treatment has provided information about the effect of drug therapy on small artery morphology (91,92). A meta-analysis of these investigations has shown that while treatment with blockers of the RAAS and calcium antagonists can reduce media-to-lumen ratio of these vessels to normotensive levels, treatment with beta-blockers has no effect; treatment with diuretics is intermediate (93). Using SLDF, treatment with aliskiren was shown to decrease retinal small artery wall-to-lumen ratio (94), while valsartan was shown to improve retinal capillary rarefaction (95). The prognostic value of reduced media-to-lumen ratio after treatment has been demonstrated using ex vivo small artery biopsies (96). Similar studies using the noninvasive SLDF or equivalent techniques are awaited.

## CONCLUSION

Structural changes in the cardiovascular system contribute to the initiation and maintenance of BP elevation in

hypertensive disease. Furthermore, structural changes in the heart and blood vessels play an important role in hypertension-induced target-organ damage. In the treatment of hypertension, prevention of target-organ damage is an increasingly important goal. We may expect that future therapies will specifically target the structural changes reviewed in this chapter.

## REFERENCES

1. Agabiti-Rosei E, Muesan ML, Schmieder RE. Cardiac damage and progression to heart failure. In: Mancia G, Grassi G, Redon J (eds) *Manual of Hypertension of the European Society of Hypertension*. Informa Healthcare, London, UK; 2014: 159–175.
2. Diamond JA, Phillips RA. Hypertensive heart disease. *Hypertens Res* 2006; 28: 191–202.
3. Molkentin JD, Lu JR, Antos CL et al. A calcineurin-dependent transcriptional pathway for cardiac hypertrophy. *Cell* 1998; 93: 215–228.
4. Deschepper CF, Boutin-Ganache I, Zahabi A, Jiang Z. In search of cardiovascular candidate genes: Interactions between phenotypes and genotypes. *Hypertension* 2002; 39: 332–336.
5. Agabiti-Rosei E, Mancia G. (eds) *Assessment of Preclinical Organ Damage in Hypertension*. Springer International Publishing, Switzerland; 2015: 3–37.
6. Perrone-Filardi P, Coca A, Galderisi M et al. Non-invasive cardiovascular imaging for evaluating subclinical target organ damage in hypertensive patients: A consensus paper from the European Association of Cardiovascular Imaging (EACVI), the European Society of Cardiology Council on Hypertension, and the European Society of Hypertension (ESH). *Eur Heart J Cardiovasc Imaging* 2017; 18: 945–960.
7. Mancia G, Fagard R, Narkiewicz et al. ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; 34(28): 2159–2219.
8. Ponikowski P, Voors AA, Anker SD et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; 37(27): 2129–2200.
9. Catena C, Colussi G, Marzano L, Sechi LA. Aldosterone and the heart: From basic research to clinical evidence. *Horm Metab Res* 2012; 44: 181–187.
10. Li YY, McTiernan CF, Feldman AM. Interplay of matrix metalloproteinases, tissue inhibitors of metalloproteinases and their regulators in cardiac matrix remodeling. *Cardiovasc Res* 2000; 46: 214–224.
11. Hsueh WA, Law RE, Do YS. Integrins, adhesion, and cardiac remodeling. *Hypertension* 1998; 31: 176–180.
12. Montezano AC, Touyz RM. Molecular mechanisms of hypertension—Reactive oxygen species and antioxidants: A basic science update for the clinician. *Can J Cardiol* 2012; 28: 288–295.
13. Cacciapuoti F. Molecular mechanisms of left ventricular hypertrophy (LVH) in systemic hypertension (SH)—possible therapeutic perspectives. *J Am Soc Hypertens* 2011; 5: 449–455.
14. Strauer BE, Motz W, Schwartzkopff B et al. The heart in hypertension. In: Swales JD (ed) *Textbook of Hypertension*. Blackwell Scientific, London; 1994: 712–731.
15. Brush JE, Cannon RO III, Schenke WH et al. Angina due to coronary microvascular disease in hypertensive patients without left ventricular hypertrophy. *N Engl J Med* 1988; 319(20): 1302–1307.
16. Muesan ML, Rizzoni D, Salvetti A et al. Structural changes in small resistance arteries and left ventricular geometry in patients with primary and secondary hypertension. *J Hypertens* 2002; 20: 1439–1446.
17. Kozakowa M, Palombo C, Pratali L et al. Mechanisms of coronary flow reserve impairment in human hypertension. An integrated approach by transthoracic and transesophageal echocardiography. *Hypertension* 1997; 29: 551–559.
18. Rizzoni D, Palombo C, Porteri E et al. Relationship between coronary vasodilator capacity and small artery remodeling in hypertensive patients. *J Hypertens* 2003; 21: 615–621.
19. Berwick ZC, Dick GM, Tune JD. Heart of the matter: Coronary dysfunction in metabolic syndrome. *J Mol Cell Cardiol* 2012; 52: 848–856.



20. Rakusan K, Hrdina PW, Turek Z et al. Cell size and capillary supply of the hypertensive rat heart: Quantitative study. *Basic Res Cardiol* 1984; 79: 389–396.
21. Struijker Boudier HA, Le Noble JL, Messing MW et al. The microcirculation and hypertension. *J Hypertens* 1992; 10: S147–S156.
22. Struijker Boudier HAJ, Van Essen H, Fazzi G et al. Disproportional arterial hypertrophy in hypertensive mRen-2 transgenic rats. *Hypertension* 1996; 28: 779–784.
23. Struijker Boudier H, Cohuet G. Mechanisms of target organ damage caused by hypertension: Therapeutic potential. *Pharmacol Ther* 2006; 111: 81–98.
24. Safar ME. Arterial stiffness as a risk factor for clinical hypertension. *Nat Rev Cardiol* 2018; 15: 97–105.
25. Lacolley M, Regnault V, Segers P, Laurent S. Vascular smooth muscle cells and arterial stiffening: Relevance in development, aging and disease. *Physiol Rev* 2017; 97: 1555–1617.
26. Snieder H, Hayward CS, Perks U et al. Heritability of central systolic pressure augmentation: A twin study. *Hypertension* 2000; 35: 574–579.
27. Laurent S, Boutouyrie P, Lacolley P. Structural and genetic bases of arterial stiffness. *Hypertension* 2005; 45: 1050–1056.
28. Palatini P, Casiglia E, Gąsowski J et al. Arterial stiffness, central hemodynamics, and cardiovascular risk in hypertension. *Vasc Health Risk Man* 2011; 7: 725–739.
29. Balkestein EJ, Wang JG, Struijker Boudier HA et al. Carotid and femoral intima-media thickness in relation to three candidate genes in a Caucasian population. *J Hypertens* 2002; 20: 1551–1561.
30. Sardana M, Vasim I, Varakantam S et al. Inactive matrix Gla-Protein and arterial stiffness in Type 2 diabetes mellitus. *Am J Hypert* 2017; 30: 196–200.
31. Gao D, Zuo Z, Tian J et al. Activation of SIRT1 attenuates Klotho deficiency-induced arterial stiffness and hypertension by enhancing AMP-activated protein kinase activity. *Hypertension* 2016; 68: 1191–1199.
32. Ku CK, Xu T, Assoian RK, Rader DJ. Mining the stiffness-sensitive transcriptome in human vascular smooth muscle cells identifies long noncoding RNA stiffness regulators. *Arterioscler Thromb Vasc Biol* 2018; 38: 164–173.
33. Laurent S. Arterial wall hypertrophy and stiffness in essential hypertensive patients. *Hypertension* 1995; 26: 355–362.
34. Safar ME, O'Rourke MF. Arterial stiffness in hypertension. In: Birkenhager WH, Reid JL (eds) *Handbook of Hypertension*. Vol 23. Elsevier, London; 2005: 1–598.
35. Duprez DA. Role of the renin-angiotensin-aldosterone system in vascular remodeling and inflammation: A clinical review. *J Hypertens* 2006; 24: 983–991.
36. Boutouyrie P, Lacolley P, Briet M et al. Pharmacological modulation of arterial stiffness. *Drugs* 2011; 71: 1689–1701.
37. Lyle AN, Raaz U. Killing me unsoftly: Causes and mechanisms of arterial stiffness. *Arterioscler Thromb Vasc Biol* 2017; 37: e1–e11.
38. Mitchell GF. Arterial stiffness: Insights from Framingham and Iceland. *Curr Opin Nephrol Hypertens* 2015; 24: 1–7.
39. De Roos A, Grond J, Mitchell G, Westenberg J. Magnetic resonance imaging of cardiovascular function of the brain. *Circulation* 2017; 135: 2178–2195.
40. Mulvany MJ, Aalkjaer C. Structure and function of small arteries. *Physiol Rev* 1990; 70: 921–961.
41. Laurent S, Boutouyrie P. The structural factor of hypertension: Large and small artery alterations. *Circ Res* 2015; 116(6): 1007–1021.
42. Rizzoni D, Agabiti-Rosei C, Agabiti-Rosei E. Hemodynamic consequences of changes in microvascular structure. *Am J Hypertens* 2017; 30(10): 939–946.
43. Aalkjaer C, Heagerty AM, Petersen KK et al. Evidence for increased media thickness, increased neuronal amine uptake, and depressed excitation-contraction coupling in isolated resistance vessels from essential hypertensives. *Circ Res* 1987; 61: 181–186.
44. Schiffrin EL. Remodeling of resistance arteries in essential hypertension and effects of antihypertensive treatment. *Am J Hypertens* 2004; 17: 1192–1200.
45. Ruedemann AD. Conjunctival vessels. *JAMA* 1933; 101: 1427–1481.
46. Antonios TF, Singer DR, Markandu ND et al. Rarefaction of skin capillaries in borderline essential hypertension suggests an early structural abnormality. *Hypertension* 1999; 34: 655–658.
47. Agabiti-Rosei E, Rizzoni D. Microvascular structure as a prognostically relevant endpoint. *J Hypertens* 2017; 35: 914–921.
48. Folkow B. Structural, myogenic, humoral and nervous factors controlling peripheral resistance. In: Harington, M (ed) *Hypotensive Drugs*. Pergamon, London; 1956: 163–174.
49. Schafer S, Kelm M, Mingers S, Strauer BE. Left ventricular remodeling impairs coronary flow reserve in hypertensive patients. *J Hypertens* 2002; 20: 1431–1437.
50. Eftekhari A, Mathiassen ON, Buus NH et al. Disproportionally impaired microvascular structure in essential hypertension. *J Hypertens* 2011; 29: 896–905.
51. Kelly R, Hayward C, Avolio A, O'Rourke M. Noninvasive determination of age-related changes in the human arterial pulse. *Circulation* 1989; 80(6): 1652–1659.
52. Muiesan ML, Salvetti M, Rizzoni D et al. Pulsatile hemodynamics and microcirculation: Evidence for a close relationship in hypertensive patients. *Hypertension* 2013; 61(1): 130–136.
53. Buus NH, Carlsen RK, Khadir DS et al. Arterial stiffness and peripheral vascular resistance in offspring of hypertensive patients: Influence of sex and other confounders. *J Hypertens* 2018; 36: 815–823.
54. Aalkjaer C, Heagerty AM, Bailey I et al. Studies of isolated resistance vessels from offspring of essential hypertensive patients. *Hypertension* 1987; 9(Suppl III): III-155–III-158.
55. Heagerty AM, Aalkjaer C, Bund SJ et al. Small artery structure in hypertension - Dual processes of remodeling and growth. *Hypertension* 1993; 21: 391–397.
56. Bruno RM, Duranti E, Ippolito C et al. Different impact of essential hypertension on structural and functional age-related vascular changes. *Hypertension* 2017; 69: 71–78.
57. Park JB, Schiffrin EL. Small artery remodeling is the most prevalent (earliest?) form of target organ damage in mild essential hypertension. *J Hypertens* 2001; 19: 921–930.
58. Intengan HD, Deng LY, Li JS, Schiffrin EL. Mechanics and composition of human subcutaneous resistance arteries in essential hypertension. *Hypertension* 1999; 33: 569–574.
59. Rizzoni D, Porteri E, Guefi D et al. Cellular hypertrophy in subcutaneous small arteries of patients with renovascular hypertension. *Hypertension* 2000; 35: 931–935.
60. Rizzoni D, Porteri E, Boari GE et al. Prognostic significance of small-artery structure in hypertension. *Circulation* 2003; 108: 2230–2235.
61. Mathiassen ON, Buus NH, Sihm I et al. Small artery structure is an independent predictor of cardiovascular events in essential hypertension. *J Hypertens* 2007; 25: 1021–1026.
62. Izzard AS, Rizzoni D, Agabiti-Rosei E, Heagerty AM. Small artery structure and hypertension: Adaptive changes and target organ damage. *J Hypertens* 2005; 23: 247–250.
63. Castorena-Gonzalez JA, Staiculescu MC, Foote C, Martinez-Lemus LA. Mechanisms of the inward remodeling process in resistance vessels: Is the actin cytoskeleton involved? *Microcirculation* 2014; 21: 219–229.
64. Huelasz-Prince G, Belkin AM, Vanbavel E, Bakker EN. Activation of extracellular transglutaminase 2 by mechanical force in the arterial wall. *J Vasc Res* 2013; 50: 383–395.
65. Van den Akker J, Van Bavel E, Van Geel R et al. The redox state of transglutaminase 2 controls arterial remodeling. *PLOS ONE* 2011; 6: e23067.
66. Umesalma S, Houwen FK, Baumbach GL, Chan SL. Roles of caveolin-1 in angiotensin II-induced hypertrophy and inward remodeling of cerebral pial arterioles. *Hypertension* 2016; 67: 623–629.
67. Schiffrin EL. Immune modulation of resistance artery remodeling. *Basic Clin Pharmacol Toxicol* 2012; 110: 70–72.
68. Heijnen BF, Nelissen J, Van Essen H et al. Irreversible renal damage after transient renin-angiotensin system stimulation: Involvement of an AT1-receptor mediated immune response. *PLOS ONE* 2013; 8: e57815.
69. Levy BI, Ambrosio G, Pries AR, Struijker-Boudier HA. Microcirculation in hypertension: A new target for treatment? *Circulation* 2001; 104: 735–740.
70. Feihl F, Liaudet L, Waeber B, Levy BI. Hypertension: A disease of the microcirculation? *Hypertension* 2006; 48: 1012–1017.
71. Le Noble FA, Stassen FR, Hacking WJ, Struijker-Boudier HA. Angiogenesis and hypertension. *J Hypertens* 1998; 16: 1563–1572.
72. Serne EH, Gans RO, Ter Maaten JC et al. Impaired skin capillary recruitment in essential hypertension is caused by both functional and structural capillary rarefaction. *Hypertension* 2001; 38: 238–242.
73. Antonios TF, Rattray FM, Singer DR, Markandu ND, Mortimer PS, MacGregor GA. Rarefaction of skin capillaries in normotensive offspring of individuals with essential hypertension. *Heart* 2003; 89: 175–178.
74. Mourad JJ, Levy BI. Mechanisms of antiangiogenic-induced arterial hypertension. *Curr Hypertens Rep* 2011; 13: 289–293.

75. Small HY, Montezano AC, Rios FJ, Savoia C, Touyz RM. Hypertension due to antiangiogenic cancer therapy with vascular endothelial growth factor inhibitors: Understanding and managing a new syndrome. *Can J Cardiol* 2014; 30: 534–543.
76. Imanishi T, Moriwaki C, Hano T, Nishio I. Endothelial progenitor cell senescence is accelerated in both experimental hypertensive rats and patients with essential hypertension. *J Hypertens* 2005; 23: 1831–1837.
77. Luo S, Xia W, Chen C, Robinson EA, Tao J. Endothelial progenitor cells and hypertension: Current concepts and future implications. *Clin Sci* 2016; 130: 2029–2042.
78. Wong TY, Mitchell P. Hypertensive retinopathy. *N Engl J Med* 2004; 351: 2310–2323.
79. Witt N, Wong TY, Hughes AD et al. Abnormalities of retinal microvascular structure and risk of mortality from ischemic heart disease and stroke. *Hypertension* 2006; 47: 975–981.
80. Cuspidi C, Sala C. Do microvascular retinal changes improve cardiovascular risk estimation? *J Hypertens* 2012; 30: 682–684.
81. Couper DJ, Klein R, Hubbard LD et al. Reliability of retinal photography in the assessment of retinal microvascular characteristics: The Atherosclerosis Risk in Communities study. *Am J Ophthalmol* 2002; 133: 78–88.
82. Liu Y, Richart T, Jin Y et al. Retinal arteriolar and venular phenotypes in a Flemish population: Reproducibility and correlates. *Artery Res* 2011; 5: 72–79.
83. Sairenchi T, Iso H, Yamagishi K et al. Mild retinopathy is a risk factor for cardiovascular mortality in Japanese with and without hypertension: The Ibaraki Prefectural Health Study. *Circulation* 2011; 124: 2502–2511.
84. Sabanayagam C, Tai ES, Shankar A et al. Retinal arteriolar narrowing increases the likelihood of chronic kidney disease in hypertension. *J Hypertens* 2009; 27: 2209–2217.
85. Ritt M, Harazny JM, Ott C et al. Analysis of retinal arteriolar structure in never-treated patients with essential hypertension. *J Hypertens* 2008; 26: 1427–1434.
86. Lehmann MV, Schmieder RE. Remodeling of retinal small arteries in hypertension. *Am J Hypertens* 2011; 24: 1267–1273.
87. Rizzoni D, Porteri E, Duse S et al. Relationship between media-to-lumen ratio of subcutaneous small arteries and wall-to-lumen ratio of retinal arterioles evaluated noninvasively by scanning laser Doppler flowmetry. *J Hypertens* 2012; 30: 1169–1175.
88. Gallo A, Mattina A, Rosenbaum D et al. Retinal arteriolar remodeling evaluated with adaptive optics camera: Relationship with blood pressure levels. *Ann Cardiol Angeiol (Paris)* 2016; 65: 203–207.
89. Rosenbaum D, Mattina A, Koch E et al. Effects of age, blood pressure and antihypertensive treatments on retinal arterioles remodeling assessed by adaptive optics. *J Hypertens* 2016; 34: 1115–1122.
90. Raff U, Harazny JM, Titze SI et al. Salt intake determines retinal arteriolar structure in treatment resistant hypertension independent of blood pressure. *Atherosclerosis* 2012; 222: 235–240.
91. Thybo NK, Korsgaard N, Eriksen S et al. Dose-dependent effects of perindopril on blood pressure and on small artery structure. *Hypertension* 1994; 23: 659–666.
92. Schiffrin EL, Deng LY, Larochelle P. Morphology of resistance arteries and comparison of effects of vasoconstrictors in mild essential hypertensive patients. *Clin Invest Med* 1993; 16: 177–186.
93. Agabiti-Rosei E, Heagerty AM, Rizzoni D. Effects of antihypertensive treatment on small artery remodelling. *J Hypertens* 2009; 27: 1107–1114.
94. Jumar A, Ott C, Kistner I et al. Effect of aliskiren on vascular remodelling in small retinal circulation. *J Hypertens* 2015; 33: 2491–2499.
95. Jumar A, Harazny JM, Ott C et al. Improvement in retinal capillary rarefaction after valsartan treatment in hypertensive patients. *J Clin Hypertens* 2016; 18: 1112–1118.
96. Buus NH, Mathiassen ON, Fenger-Gron M et al. Small artery structure during antihypertensive therapy is an independent predictor of cardiovascular events in essential hypertension. *J Hypertens* 2013; 31: 791–797.



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## HUMAN AGEING IN PERSPECTIVE

The biological ageing of humans is shaped by evolutionary selection and represents a compromise between reproductive fitness, longevity, and the genetic regulation of organ function. It is also influenced by environmental (epigenetic) factors (1). The maximum recorded human lifespan is 122 in Jeanne Calment (1875–1997), a French woman. Normally competing mortality risks will contribute to shape the demographic structure of a given population, both mean and maximum lifespan. The demographic transition has occurred in modern societies when lifespan has been prolonged and deaths no longer are caused by infectious disease and malnutrition, but to a larger extent by noncommunicable diseases (NCD) such as cardiovascular disease, type 2 diabetes, cancer, dementia and chronic obstructive pulmonary disease (COPD).

A reflection of the biological ageing in general is the *vascular ageing* process, as shaped by genetic factors, early life programming, lifestyle and comorbidities. The large elastic arteries undergo a typical process of increasing arterial stiffness (*arteriosclerosis*) with ageing. Thus, arterial stiffness of the aorta or carotid arteries is the hallmark of arterial ageing, further increased by hypertension (2). This process starts in the arterial media, as different from *atherosclerosis* that starts in the arterial intima. Later in life the two pathologies become intertwined and increase the risk of cardiovascular events, as evident from numerous epidemiological studies and meta-analyses (3,4).

## HISTORICAL NOTES ON ARTERY RESEARCH LEADING TO EARLY VASCULAR AGEING

In a historical perspective, the interest in arterial function and stiffness contributing to hemodynamic changes predates the clinical measurement of blood pressure and diagnosis of hypertension as we know it. In London, UK,

the physician Frederick Akbar Mahomed carried out studies on pulse wave properties in *arteria radialis* with his own constructed sphygmograph, and published in 1877:

It is very common to meet with people apparently in good health who have no albumen in the urine, who constantly present a condition of high arterial tension when examined by the aid of the sphygmograph (5).

In more recent times but bridging back to the previous researchers on arterial function, the concept of early vascular ageing (EVA) was introduced to describe the early ageing of large elastic arteries (6–11) but widened the perspective to other vascular beds. The core component of EVA is large artery stiffening that exceeds what is expected from normal ageing. Indeed, large arteries stiffen with ageing (mechanisms are detailed below). Thus, EVA is defined as an abnormally high arterial stiffness for a given age. Arterial stiffness is the consequence of arteriosclerosis, which is mainly influenced by morphological changes in the arterial media layer, but also in other layers. EVA should be considered based on an integrated view linking the macro- with the microcirculation. This is because hemodynamic forces influenced by stiffness may also cause harm to the peripheral smaller vessels due to the increased pulsatile energy that is transmitted, for example in the brain (12). Another aspect of a more integrated approach identifies important contributing factors for EVA also from the arterial intima (endothelial dysfunction) and the adventitia (impaired function of vasa vasorum and innervation, and increased secretion of cytokines from the perivascular adipose tissue causing local inflammation) when impaired glucose metabolism (hyperglycaemia) could further contribute to stiffening by glycosylation. Therefore, we consider EVA to be a fruitful scientific concept to promote research on early changes of the arterial wall, eventually programmed already in utero and early life, and influenced by genetic and environmental factors in a life course perspective (6) (Figure 11.1 and Table 11.1).

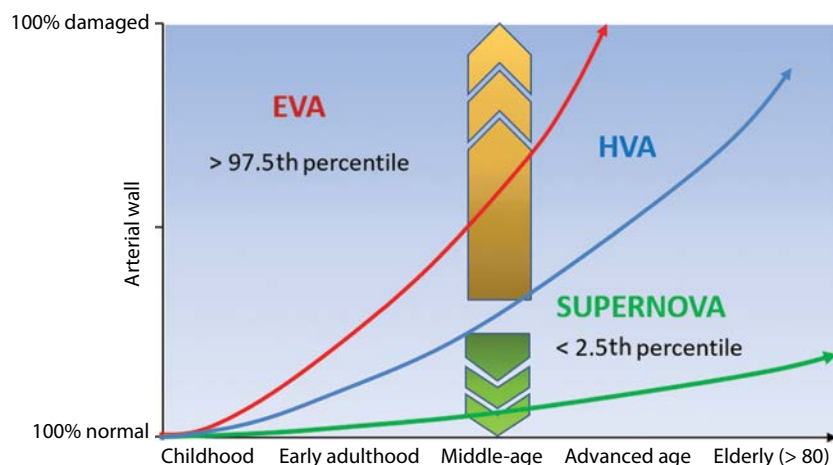


**Figure 11.1** Healthy vascular ageing (HVA), early vascular ageing (EVA) and supernormal vascular ageing (SUPERNOVA), determined as a function of arterial wall damage according to age. EVA can be defined as an aortic pulse wave velocity (aPWV) more than 2 standard deviations *above* the predicted value for a certain age and sex within a defined population (i.e. higher than the 97.5th percentile of aPWV). SUPERNOVA can be defined as aPWV more than 2 standard deviations *below* the predicted value for a certain age and sex within a defined population (i.e. lower than the 2.5th percentile of aPWV).

**Table 11.1** Determinants of early vascular ageing (EVA)

| Nonmodifiable                                                                                                                     | Modifiable                 |                                                                                                                                                                                                                                                   |
|-----------------------------------------------------------------------------------------------------------------------------------|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Ethnicity</b><br><b>Sex</b><br><b>Chronological age</b><br><b>Family history</b><br><b>Genetics</b><br><b>Personal history</b> | Classical CV risk factors  | Blood pressure<br>Hyperglycaemia/insulin resistance/DM<br>Obesity/abdominal fat<br>Metabolic syndrome<br>Dyslipidemia<br>Smoking<br>Sedentarity, lack of physical activity                                                                        |
|                                                                                                                                   | Additional CV risk factors | High salt<br>Chronic low-grade inflammation<br>Oxidative stress<br>Social deprivation<br>Perceived stress<br>Inadequate diet<br>Alcohol consumption<br>Abnormal sleep pattern<br>Thrombogenic factors<br>UVA and UVB radiation<br>Hormonal status |

## THE RISK OF ARTERIAL STIFFNESS FOR TOTAL MORTALITY AND CARDIOVASCULAR EVENTS

Two meta-analyses have documented that arterial stiffness (increased aortic pulse wave velocity [aPWV]) is an independent risk marker for future cardiovascular risk and total mortality, adjusted for conventional risk factors including blood pressure (3,4). We therefore consider it of importance to find new ways to find, diagnose and treat subjects with signs of EVA. Still, however, neither an exact definition nor a targeted treatment exist for EVA, but several attempts are being made to find such alternatives. Data describing EVA are needed from different populations and ethnic groups, as well as data from basic and

clinical science (8). This could contribute to early detection of risk individuals; for example, from risk families with early-onset cardiometabolic disease (13), for cardiovascular prevention based on improved lifestyle as well as drug therapy when needed. This is not to deny the importance of atherosclerosis and the evidence-based methods that exist to prevent cardiovascular events by control of hypertension and hyperlipidaemia as well as smoking cessation. We, however, consider that EVA, as mirrored by changes in central hemodynamics, is a feature starting early in life (6), and that later in life components of arteriosclerosis and atherosclerosis will act synergistically to increase cardiovascular disease risk.

We therefore date the interest in large arteries and stiffness to an era before clinical hypertension was recognized (14), and thus the EVA concept (6–11) attempts



to bridge more than a century to revive the importance of large arteries and their properties in cardiovascular medicine.

## THE EMERGENCE OF THE EVA CONCEPT AND ATTEMPTS MADE TO DEFINE IT

Arterial stiffness has been accumulating evidence as an intermediate cardiovascular endpoint. It has been established as an independent risk marker for cardiovascular disease and reflects the dissociation between chronologic and biologic age of large arteries, causing the earlier development of cardiovascular risk that normal vascular ageing could induce several years later (10). The EVA concept is developed to establish primordial prevention, identifying individuals whose ageing path has been accelerated either by inherent features, interaction with the environment, or arterial exposure to several types of insults that evolve to medial layer morphological changes. Understanding the pathophysiology of vascular ageing, its consequences and therapeutic opportunities, is therefore an advantage that could be translated in time of prevention and survival free of cardiovascular disease. As the EVA construct is advancing, new features appear as interesting to better translate it into clinical practice (10), particularly through gold standard measurements (15) and reference values (16).

Attempts have been made to define EVA. The most useful is perhaps to define it as aPWV more than 2 standard deviations above the predicted value (i.e. higher than the 97.5th percentile of aPWV) for a certain age and sex within a defined population (10) or based on a large European database of healthy, normotensive individuals (16). Even the out-of-proportion remodelling of the aorta, as visible from magnetic resonance imaging (MRI), has been regarded as a marker of vascular ageing (17), a phenomenon most pronounced in the thoracic part of the aorta and in, for example, female patients with Turner (45, X0) syndrome (18).

## MOLECULAR MECHANISMS BEHIND ARTERIAL STIFFNESS AND MECHANOTRANSDUCTION

It is important to develop a deeper understanding of the molecular basis of arterial stiffness in order to find new treatment targets beyond conventional risk factor control. A recent review has summarized the state-of-the-art knowledge in this area (19). Although it is generally accepted that the major components that contribute to arterial stiffening are extracellular matrix (ECM) proteins, such as elastin and collagens, a second important component is vascular smooth muscle cells (VSMCs), the role of which has been highlighted more recently. VSMCs not only regulate actomyosin interactions for contraction but also mediate mechanotransduction in cell-ECM homeostasis. Both VSMC contraction and changes in cell-ECM interaction, for instance through the architecture of cytoskeletal proteins and focal adhesions, can transfer the mechanical load from elastic components to stiff components, and thus increase the stiffness of the wall material. VSMCs plasticity and signalling can affect both conductance and

resistance arteries, and thus increase arterial stiffness and induce arteriolar remodelling, respectively. In response to this large/small artery cross-talk (20), central blood pressure and tensile pulsatile circumferential stress are increased. Thus, a feedback mechanism (21) is developed, since central pressure and tensile pulsatile circumferential stress act as key mechanical determinants of arterial wall remodelling and cell-ECM interactions. Lacolley et al. (19) have speculated on the contribution of cellular stiffness along the arterial tree to vascular wall stiffness (18). Now that important hemodynamic and molecular mechanisms of arterial stiffness have been elucidated and the complex interplay between ECM, cells, and sensors identified, further research should study their potential to halt or reverse the development of arterial stiffness.

## GENETICS OF ARTERIAL STIFFNESS AND THE ROLE OF GLYCAEMIA

In the review by Lacolley et al., a summary of the evidence linking genetic factors to arterial stiffness has been provided (19). This is an expanding area of research and could contribute to finding causal pathways influencing arterial stiffness based on Mendelian randomization methodology. New and very recent data indicate that a genetic risk score (GRS) for a hyperglycaemic trait, separate from GRSs linked to type 2 diabetes, hypertension or hyperlipidaemia, is significantly associated with aPWV in an elderly Swedish population (22), thereby strengthening the link between impaired glucose metabolism and increased arterial stiffness that a number of observational, epidemiological studies have also been reported (23,24). Increased aPWV is even a risk marker for future incidence of type 2 diabetes in the same population (25).

## CHRONIC INFLAMMATION

Another important aspect of vascular ageing is the influence of chronic low-grade inflammation. Large artery stiffening has been reported during various diseases associated with chronic low-grade inflammation, such as rheumatoid arthritis, systemic lupus erythematosus, systemic vasculitis, human immunodeficiency virus and inflammatory bowel disease (26,27). In a population-based study, it was shown that inflammatory markers at baseline predicted the development of arterial stiffness during follow-up (28). Various mechanisms have been suggested, including endothelial dysfunction, activation of VSMC-mineralocorticoid receptor related to ANG II, cell release of a number of inducible matrix metalloproteinases, elastocalcinosis and accumulation of proteoglycans in the media, and finally adventitial immune cells and cytokines released from the vasa vasorum in response to vessel ischemia (29).

## COGNITION – BRAIN AGEING

The process of vascular ageing is also reflected by brain ageing and cognitive decline. Subjects with increased arterial stiffness are more prone to deteriorate according to cognitive function over time (30), and to show more abnormalities by

brain magnetic resonance imaging (31). In a recent study it was shown that the relationship between increasing aPWV and cognitive impairment is nonlinear when adjusted for other risk factors, thus indicating a cognitive reserve that is protected until arterial stiffness (pulse wave velocity [PWV]) is considerably increased, at least in an elderly population that might have been health-selected (32).

## NEW RESEARCH DIRECTIONS – HVA AND SUPERNOVA

In more recent studies, the interest has shifted also to the concept of healthy vascular ageing (HVA) and its determinants in defined population, as shown in a French cohort (33), as well as in the Framingham Heart Study (34). In the latter, HVA was defined by lack of hypertension in combination with low values of aPWV for groups stratified by age range (34). This definition could, however, also be questioned, as a subject with elevated blood pressure that could be due to white-coat effect at the measurement, and a relatively low PWV, would not be labelled with HVA, even if this could be relevant. Subjects with previous CVD manifestations do not have HVA and should preferably be excluded from analyses of determinants of HVA. On the other hand, we know that increased arterial stiffness is a predictor of incident hypertension (35). This is why these relationships are not easy to disentangle. In clinical practice, HVA can be measured by aPWV (Figure 11.1). Because large arteries stiffen with ageing, any value of aPWV should be interpreted as a function of age. Thus, in a given subject, HVA corresponds to the aPWV that is expected from his/her age in a population with no cardiovascular risk factor (16).

Recently, we advanced the concept of SUPERNOVA (supernormal vascular ageing) in order to promote interest in targeting not only individuals with accelerated vascular ageing, but also the very few who had limited vascular ageing, for instance those with a low aPWV for a given age (Figure 11.1 and Table 11.2). SUPERNOVA can be defined as aPWV more than 2 standard deviations below the predicted value (i.e. lower than the 2.5th percentile of aPWV) for a certain age and sex within a defined population (10) or based on a large European database of healthy, normotensive individuals (16). We are convinced that major scientific achievements can be obtained by looking at the two extreme parts of the distribution (upward and downward shifts) of the age/stiffness relationships. A small number of cohort studies in remote populations have shown that arterial stiffness does not necessarily increase with ageing. For instance, Lemogoum et al. (36) have shown that the effect of ageing and blood pressure on arterial stiffness is blunted in Cameroon traditional pygmies on hunter-gather subsistence mode, whereas this is not the case in contemporary pygmies who migrated to semi-urban areas, or Bantou farmers. The hunter-gather lifestyle is associated with lower body weight, mean blood pressure, and LDL-cholesterol which are likely translated into lower aortic stiffness. Furthermore, Hollenberg et al. (37) have shown that the Kuna Indians, who reside in an archipelago on the Caribbean Coast of Panama, have very low blood pressure levels, live longer than other Panamanians, and have a reduced frequency of myocardial infarction, stroke and diabetes mellitus. One outstanding feature of their diet includes a very high intake of flavanol-rich cocoa, which

**Table 11.2** Determinants of supernormal vascular ageing (SUPERNOVA)

| Nonmodifiable            | Modifiable                    |                                   |
|--------------------------|-------------------------------|-----------------------------------|
| <b>Ethnicity</b>         | No classical CV risk factors  | Normal blood pressure             |
| <b>Sex</b>               |                               | Normal glycaemia                  |
| <b>Chronological age</b> |                               | Normal weight                     |
| <b>Family history</b>    |                               | Low lipids                        |
| <b>Genetics</b>          |                               | Low salt                          |
| <b>Personal history</b>  | No additional CV risk factors | Calorie restriction               |
|                          |                               | No smoking                        |
|                          |                               | Intense physical activity         |
|                          |                               | No perceived stress               |
|                          |                               | No social deprivation             |
|                          |                               | Normal sleep pattern              |
|                          |                               | No thrombogenic factors           |
|                          |                               | Normal prenatal fetal growth      |
|                          |                               | Adequate UVA and UVB radiation    |
|                          |                               | Normal hormonal status            |
|                          | Strong protective mechanisms  | No inflammation                   |
|                          |                               | Insensitivity to oxidative stress |

suggests that sustained nitric oxide activation protect the Kuna Indians from common causes of morbidity and mortality. An interesting animal model of SUPERNOVA is the naked mole-rat (NMR; *Heterocephalus glaber*), that has a maximum lifespan potential of more than 30 years, very low blood pressure levels and does not increase PWV with ageing (38). The natural subterranean habitat of the NMR is thought to have shaped the species' upregulated cellular stress resistance and protection. NMRs have a constitutive upregulation of nuclear factor erythroid 2-related factor 2 (Nrf2), thus an increased transcription of numerous antioxidants, detoxicants, molecular chaperons and protease components (38).

Future research directions can be summarized as follows. In mouse models of supernormal or extreme vascular ageing, a better understanding of the molecular pathways of VSMC senescence is required as well as a detailed analysis of arterial mechanics, and heart, brain and kidney functions. The discovery of novel molecular pathways may lead to novel drugs. In humans, a detailed epidemiological analysis of healthy ageing and supernormal ageing is necessary, including a large number of possible determinants. The influence of telomere length on arterial ageing should also be further studied. Eventually, novel drugs should be studied in clinical pharmacology.

## INTERVENTIONS THAT RETARD VASCULAR AGEING

Several types of interventions can target a large number of EVA determinants, as exemplified in Table 11.1. Particularly, prevention strategies targeting modifiable factors such as elevated blood pressure, behaviours and obesity should be organized at the population level, to prevent or delay vascular ageing and the associated risk of cardiovascular

complications. In particular, calorie restriction and moderate physical activity are recommended in primordial prevention, even if it is often difficult for individuals to accept. Calorie restriction is one of the most effective among the potential interventions that retard vascular ageing (39). Calorie restriction has been reproducibly shown to improve endothelial function, prevent atherosclerosis and arterial stiffening, reduce myocardial interstitial fibrosis and cardiac apoptosis, improve cardiac function and prolong lifespan in various experimental model animals (39). Calorie restriction also confers significant microvascular protection by improving endothelial angiogenic capacity, increasing cortical microvascular density, and restoring microvascular nitric oxide synthesis, all of which enhance the metabolism of parenchymal tissues.

Niiranen et al. (34) assessed the prevalence, correlates and prognosis of HVA in 3196 Framingham Study participants aged  $\geq 50$  years during a follow-up of 9.6 years. In Cox regression models adjusted for traditional cardiovascular risk factors, including blood pressure, they showed that HVA was associated with a hazard ratio of 0.45 (95% confidence interval, 0.26–0.77) for cardiovascular events relative to absence of HVA. However, although HVA is achievable in individuals acculturated to a Western lifestyle, maintaining normal vascular function at an older age is challenging.

Pharmacological interventions are also needed. Calorie restriction mimetics, developed from the laboratory animals and epidemiological evidence for the effectiveness of calorie restriction, may be soon available, at least in preclinical drug development (39). They target several key signalling pathways implicated in calorie restriction-mediated cardiovascular protection, and include Sirt1 activators, adenosine monophosphate-activated protein kinase activators, mechanistic target of rapamycin inhibitors and NRF2 activators (39). Whether they can reach the clinical drug development level remains an open issue. Antiplatelet agents as well as antihypertensive, lipid-lowering and antidiabetic drugs, are effective but have no indication at an earlier stage. This applies also to antihypertensive drugs in development (40). Among novel drugs targeting the renin-angiotensin system, the AT2-receptor agonist Compound 21 (C21) attracted attention since it acts blood pressure-neutral. However, AT2-receptor stimulation is still able to significantly prevent hypertensive end-organ damage, improve neurological outcome after stroke or prevent pulmonary hypertension in a pulmonary fibrosis model. For example, two independent studies showed that in hypertensive rats, C21 prevented vascular stiffening and collagen accumulation resulting in a reduction of PWV despite persisting elevated blood pressure levels (41). This blood pressure-independent antifibrotic effect may be of interest in primary prevention.

## SUMMARY

The concept of EVA has attracted increased attention in recent years, and aPWV as an imaging biomarker of arterial stiffness, the core component of EVA, has been emphasized in guidelines, for example from the European Society of Hypertension (42). Furthermore, the recent Lancet Hypertension Commission used the EVA concept to promote early screening and treatment of hypertension and

other risk factors to influence risk in a life course perspective (43). Finally, new ways to understand biological ageing in general, and vascular ageing in particular, could contribute to a better understanding and identification of new treatment targets. For example, studies on telomere length and impaired glucose metabolism in relation to PWV could bring new knowledge. In the end we should, however, focus not only on risk associated with PWV and EVA in various populations, and corresponding treatment, but also on HVA and SUPERNOVA to learn more about vascular protection.

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## REFERENCES

- Otten AB, Smeets HJ. Evolutionary defined role of the mitochondrial DNA in fertility, disease and ageing. *Hum Reprod Update* 2015; 21(5): 671–689.
- Najjar SS, Scuteri A, Lakatta EG. Arterial ageing: Is it an immutable cardiovascular risk factor? *Hypertension* 2005; 46(3): 454–462.
- Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: A systematic review and meta-analysis. *J Am Coll Cardiol* 2010; 55(13): 1318–1327.
- Ben-Shlomo Y, Spears M, Boustred C et al. Aortic pulse wave velocity improves cardiovascular event prediction: An individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol* 2014; 63: 636–646.
- Mahomed FA. Remarks on arterio-capillary fibrosis and its clinical recognition. *Lancet* 1877; 110(2816): 232–234.
- Nilsson PM, Lurbe E, Laurent S. The early life origin of vascular ageing and cardiovascular risk. *J Hypertens* 2008; 26: 1049–1057.
- Nilsson PM, Boutouyrie P, Laurent S. Vascular ageing: A tale of EVA and ADAM in cardiovascular risk assessment and prevention. *Hypertension* 2009; 54: 3–10.
- Nilsson PM, Boutouyrie P, Cunha P et al. Early vascular ageing in translation: From laboratory investigations to clinical applications in cardiovascular prevention. *J Hypertens* 2013; 31: 1517–1526.
- Cunha PG, Cotter J, Oliveira P et al. Pulse wave velocity distribution in a cohort study: From arterial stiffness to early vascular ageing. *J Hypertens* 2015; 33(7): 1438–1445.
- Cunha PG, Boutouyrie P, Nilsson PM, Laurent S. Early vascular ageing (EVA): Definitions and clinical applicability. *Curr Hypertens Rev* 2017; 13(1): 8–15.
- Kotsis V, Antza C, Doundoulakis I, Stabouli S. Markers of early vascular ageing. *Curr Pharm Des* 2017; 23(22): 3200–3204.
- Scuteri A, Nilsson PM, Tzourio C et al. Microvascular brain damage with ageing and hypertension: Pathophysiological consideration and clinical implications. *J Hypertens* 2011; 29(8): 1469–1477.
- Fatehali AA, Gottsäter M, Nilsson PM. Family history of cardio-metabolic diseases and its association with arterial stiffness in the Malmö Diet Cancer cohort. *J Hypertens* 2017; 35(11): 2262–2267.
- Riva-Rocchi S. Un nuovo sfigmomanometro. *Gazz Med Torino* 1896; 50–51: 1001–1007.
- Laurent S, Marais L, Boutouyrie P. The non-invasive assessment of vascular aging. *Can J Cardiol* 2016; 32: 669–679.
- Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J* 2010; 31(19): 2338–2350.
- Tosello F, Leone D, Laurent S et al. Out of proportion proximal aortic remodeling: A subclinical marker of early vascular ageing? A systematic review. *Int J Cardiol* 2016; 223: 999–1006.
- Devos DG, De Groote K, Babin D et al. Proximal aortic stiffening in Turner patients may be present before dilation can be detected: A segmental functional MRI study. *J Cardiovasc Magn Reson* 2017; 19(1): 27.
- Lacolley P, Regnault V, Segers P, Laurent S. Vascular smooth muscle cells and arterial stiffening: Relevance in development, aging, and disease. *Physiol Rev* 2017; 97(4): 1555–1617.

20. Laurent S, Briet M, Boutouyrie P. Large/small artery cross talk and recent morbidity mortality trials in hypertension. *Hypertension* 2009; 54: 388–392.
21. Humphrey JD, Harrison DG, Figueroa CA et al. Central artery stiffness in hypertension and aging: A problem with cause and consequence. *Circ Res* 2016; 118: 379–381.
22. Gottsäter M, Hindy G, Orho-Melander M et al. A genetic risk score for fasting plasma glucose is independently associated with arterial stiffness: A Mendelian randomization study. *J Hypertens* 2018; 36(4): 809–814.
23. Gottsäter M, Östling G, Persson M et al. Non-hemodynamic predictors of arterial stiffness after 17 years of follow-up: The Malmö Diet and Cancer study. *J Hypertens* 2015; 33(5): 957–965.
24. van Eupen MG, Schram MT, van Sloten TT et al. Skin autofluorescence and pentosidine are associated with aortic stiffening: The Maastricht study. *Hypertension* 2016; 68(4): 956–963.
25. Muhammad IF, Borné Y, Östling G et al. Arterial stiffness and incidence of diabetes: A population-based cohort study. *Diabetes Care* 29 September 2017. pii: dc171071. doi: 10.2337/dc17-1071.
26. Roman MJ, Devereux RB, Schwartz JE et al. Arterial stiffness in chronic inflammatory diseases. *Hypertension* 2005; 46: 194–199.
27. Zanolli L, Boutouyrie P, Fatuzzo P et al. Inflammation and aortic stiffness: An individual participant data meta-analysis in patients with inflammatory bowel disease. *J Am Heart Assoc* 2017; 6(10).
28. Muhammad IF, Borné Y, Östling G et al. Acute phase proteins as prospective risk markers for arterial stiffness: The Malmö Diet and Cancer cohort. *PLOS ONE* 2017; 12(7): e0181718.
29. Laurent S, Boutouyrie P. The structural factor in hypertension: Large and small artery alterations. *Circ Res* 2015; 116: 1007–1021.
30. Scuteri A, Tesaro M, Appolloni S et al. Arterial stiffness as an independent predictor of longitudinal changes in cognitive function in the older individual. *J Hypertens* 2007; 25(5): 1035–1040.
31. Mitchell GF, van Buchem MA, Sigurdsson S et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: The Age, Gene/Environment Susceptibility—Reykjavik study. *Brain* 2011; 134(Pt 11): 3398–3407.
32. Nilsson ED, Elmståhl S, Minthon L et al. Nonlinear association between pulse wave velocity and cognitive function: A population-based study. *J Hypertens* 2014; 32(11): 2152–2157, discussion 2157.
33. Gaye B, Mustafic H, Laurent S et al. Ideal cardiovascular health and subclinical markers of carotid structure and function: The Paris Prospective Study III. *Arterioscler Thromb Vasc Biol* 2016; 36(10): 2115–2124.
34. Niiranen TJ, Lyass A, Larson MG et al. Prevalence, correlates, and prognosis of healthy vascular ageing in a Western community-dwelling cohort: The Framingham Heart Study. *Hypertension* 2017; 70(2): 267–274.
35. Kaess BM, Rong J, Larson MG et al. Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA* 2012; 308(9): 875–881.
36. Lemogoum D, Ngatchou W, Janssen C et al. Effects of hunter-gatherer subsistence mode on arterial distensibility in Cameroonian pygmies. *Hypertension* 2012; 60: 123–128.
37. Hollenberg NK, Fisher ND, McCullough ML. Flavanols, the Kuna, cocoa consumption, and nitric oxide. *JASH* 2009; 3: 105–112.
38. Grimes KM, Reddy AK, Lindsey ML, Buffenstein R. And the beat goes on: Maintained cardiovascular function during aging in the longest-lived rodent, the naked mole-rat. *Am J Physiol Heart Circ Physiol* 2014; 307: H284–H291.
39. Alfaro I, Di Germanio C, Bernier M et al. Pharmacological strategies to retard cardiovascular aging. *Circ Res* 2016; 118: 1626–1642.
40. Laurent S, Schlaich M, Esler M. New drugs, procedures, and devices for hypertension. *Lancet* 2012; 380(9841): 591–600.
41. Paulis L, Becker ST, Lucht K et al. Direct angiotensin II type 2 receptor stimulation in N<sup>ω</sup>-nitro-L-arginine-methyl ester-induced hypertension: The effect on pulse wave velocity and aortic remodeling. *Hypertension* 2012; 59(2): 485–492.
42. Williams B, Mancia G, Spiering W et al. Authors/Task Force Members: 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens* 2018; 36(10): 1953–2041.
43. Olsen MH, Angell SY, Asma S et al. A call to action and a life-course strategy to address the global burden of raised blood pressure on current and future generations: The Lancet Commission on Hypertension. *Lancet* 2016; 388(10060): 2665–2712.



*Gino Seravalle and Guido Grassi*

## INTRODUCTION

The progression from the early stage to the more severe hypertensive state, without or with target-organ damage or associated to metabolic disorders, is accompanied by autonomic dysfunction as one of the main pathophysiological mechanisms. Several other factors may be involved, but the metabolic one, and the insulin resistance in particular, appears to be the leading candidate. This chapter reviews the main evidence related to the relationship between autonomic dysfunction and the hypertensive state during the progression to more complicated conditions.

## AUTONOMIC DYSFUNCTION AND THE HYPERTENSIVE STATE

It has been clearly shown by evidence collected throughout the years that essential hypertension is characterized by a reduction in the inhibitory influences exerted by the vagus on the heart and by a concomitant participation of the adrenergic neurotransmitters on the sinus node (1,2). The tachycardic response appears to be the first evidence of autonomic dysfunction in young hypertensive individuals (the so-called hyperkinetic syndrome) and in the earlier stage of the hypertensive state (1–4).

Evidence for an autonomic imbalance comes from studies obtained with different approaches (plasma catecholamine levels, spectral analysis of the R-R interval, catecholamines spillover, microneurographic recordings of muscle sympathetic nerve traffic) in the early phases of hypertension and also in the pre-hypertensive state, or in normal subjects with a family history of hypertension (1,2,5–8).

Studies in the normotensive offspring of hypertensive parents have shown the presence of a sympathetic hyperactivity that is accompanied by an impaired vagal influence on the heart (7,8). Studies with radiolabeled norepinephrine have extended the observations made in pre-hypertensive conditions to borderline hypertension (9). This has been confirmed by microneurographic recordings of the efferent postganglionic sympathetic nerve fibres in young individuals with either a high-normal blood pressure or borderline hypertension (10–12) (Table 12.1).

A progressive adrenergic hyperactivity is evident with the progression of the hypertensive state and it is particularly pronounced in more established and advanced

stages of the disease that is systodiastolic hypertension, isolated systolic hypertension and resistant hypertension (13–15). The permanent increase of sympathetic drive also generates a down-regulation of peripheral  $\beta$ -adrenergic receptors (16) that may partly offset the consequences of sympathetic hyperactivation. The increase of the adrenergic tone has also been documented in other physiological conditions such as in elderly subjects and in the pregnancy-induced hypertension (1,2,15,17). An interesting observation is that in secondary forms of hypertension, such as in pheochromocytoma, adrenergic tone does not increase due to activation of the inhibitory baroreflex influences (13).

A sympathetic activation could also be observed in subjects who present a white-coat effect or a masked hypertension, a condition in which blood pressure taken in the doctor's office is normal, while it is increased at home (18,19). It has been established that both these conditions have a marked risk of progressing to an established hypertensive state and to an increased cardiovascular risk (20). To this aim is debated the need for a treatment but the increased cardiovascular risk of these subjects suggests for a positive answer.

Alteration in blood pressure profile during sleep is not accompanied by important changes in sympathetic outflow despite the higher cardiovascular risk in non-dippers than in dippers (21). The observation of snoring and hypoxia during sleep is different. In this case, the reflex mechanisms under chemoreceptor control have shown to greatly influence the adrenergic tone and to increase the morbidity of these subjects (22). Different approaches have been suggested in these cases such as application of systems to maintain positive pressure in the airways or to modify the mouth closure, or surgical approaches to remodel pharyngeal structures.

## AUTONOMIC DYSFUNCTION AND HYPERTENSION-RELATED ORGAN DAMAGE

Several studies performed with outstanding methodologies have clearly shown that the hyperadrenergic tone that characterizes essential hypertension is not stable but follows a progression from uncomplicated to complicated stages (13). Compared to respective controls, the increase



**Table 12.1** Adrenergic tone in conditions characterized by or associated with hypertension

| Condition                 | MSNA | Plasma norepinephrine |
|---------------------------|------|-----------------------|
| Pre-hypertension (7,8,10) | ↑    | ↑                     |
| Systo-diastolic HT (15)   | ↑    | ↑                     |
| HT mild (9,13)            | ↑    | ↑                     |
| HT severe (9,13)          | ↑    | ↑                     |
| Isolated systolic HT (15) | ↑    | ↑ =                   |
| Resistant HT (14)         | ↑    | ↑ =                   |
| White-coat HT (18,20)     | ↑    | ↑                     |
| Masked HT (19,20)         | ↑    | ↑                     |
| HT and pregnancy (17)     | ↑    | ↑ =                   |
| HT and obesity (40,41)    | ↑    | ↑ =                   |
| HT and OSAS (22,40)       | ↑    | ↑                     |
| HT and LVH (26)           | ↑    | ↑                     |
| HT and CHF (25,27,36)     | ↑    | ↑                     |
| HT and CKD (24)           | ↑    | ↑                     |

Abbreviations: HT, hypertension; OSAS, obstructive sleep apnea syndrome; LVH, left ventricular hypertrophy; CHF, congestive heart failure; CKD, chronic kidney disease.

in the adrenergic tone is more pronounced in hypertensive subjects with impaired renal function (23,24) or with alterations in cardiac structure or function (25,26). This is also evident in hypertensive patients who do not respond to antihypertensive drug administration—the so-called resistant hypertensives (14). This consistent amount of data suggests that activation of the sympathetic nervous system is parallel with the progressive increase in blood pressure values and the development of organ damage or the appearance of clinical evidence of renal and cardiac disease. Associations do not mean cause-effect relationships, thus is necessary to know whether the increased sympathetic tone accompanying the progressive hypertensive state has a pathogenetic role. Data are available that hyperadrenergic tone, independently by blood pressure changes, is able to favour alterations in cardiac and vascular structure (28,29). This was evident not only in experimental studies but also in human studies. Anaesthesiologic nerve block in patients undergoing orthopaedic surgery was followed by a marked reduction in ipsilateral artery stiffness in the absence of blood pressure changes, with a return to control values after reinnervation (30,31). This is also the case for the hypertension-related vascular alterations in which a reduced arterial compliance could be associated with an impaired endothelial function and a vascular remodelling and hypertrophy which favour the development of the atherogenic plaque (32).

Data collected from norepinephrine spillover in different cardiovascular districts have shown in the hypertensive state a greater increase in the cerebral, coronary and renovascular districts (9). This, of course, has important

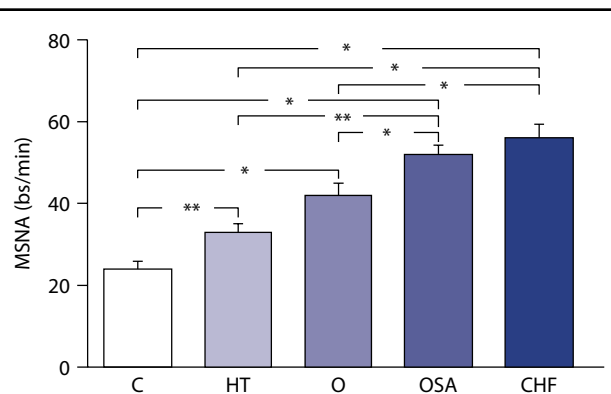


**Figure 12.1** Muscle sympathetic nerve activity expressed as bursts frequency over time in healthy controls and in patients with hypertension (HT), obesity (O), obstructive sleep apnea (OSA), and congestive heart failure (CHF). \* $p < 0.05$ , \*\* $p < 0.01$  in a comparison between groups. Data are shown as the mean  $\pm$  SE. (Redrawn with data derived from Grassi G et al. *Hypertension* 1998; 31: 68–72; Grassi G et al. *Circulation* 1995; 92: 3206–3211; Grassi G et al. *J Hypertens* 2014; 32: 383–388. References (13),(36),(40).)

clinical implications. Several studies have clearly shown that a progressive increase in adrenergic tone is present when the hypertensive state induces a negative evolution in cardiac function from cardiac hypertrophy to left ventricular dilation (Figure 12.1). The marked sympathetic activation that follows the progressive deterioration of heart function, which induces an activation of several reflex and neurohumoral mechanisms, can be used as a predictor of cardiovascular morbidity and mortality (33,34). The close dependency of the sympathetic overactivity on baroreflex alterations, with the progressive loss of the inhibitory effects exerted by this reflexogenic area on central sympathetic outflow, is particularly evident during the progression from mild to severe heart failure state (35,36). In relation to the different autonomic involvement in cardiovascular districts, it is also possible to extend this predictive ability to other pathophysiological conditions that present an activation of the sympathetic nervous system as a common factor (37–39).

Several studies have also investigated the autonomic profile in metabolic disease that frequently coexists with hypertension. The hypertensive state associated with an increased visceral fat distribution shows signs of adrenergic activation such as an increased resting heart rate and elevated plasma norepinephrine levels. This has been confirmed by the direct evidence of augmented sympathetic nerve traffic and increased catecholamine spillover, particularly at the kidney level, in obese subjects (40,41). In obese hypertensives, the neurogenic alterations originate from an impairment of the reflex control involving all the reflexogenic areas (baroreceptors, cardiopulmonary receptors and chemoreceptors). In this condition the other metabolic, neurohumoral, inflammatory alterations also appear to be greatly activated, and in particular the significant relationship between increase in insulin resistance and activation of the sympathetic nervous system is clearly shown (40).

## AUTONOMIC DYSFUNCTION IN HYPERTENSION: PATHOPHYSIOLOGICAL MECHANISM

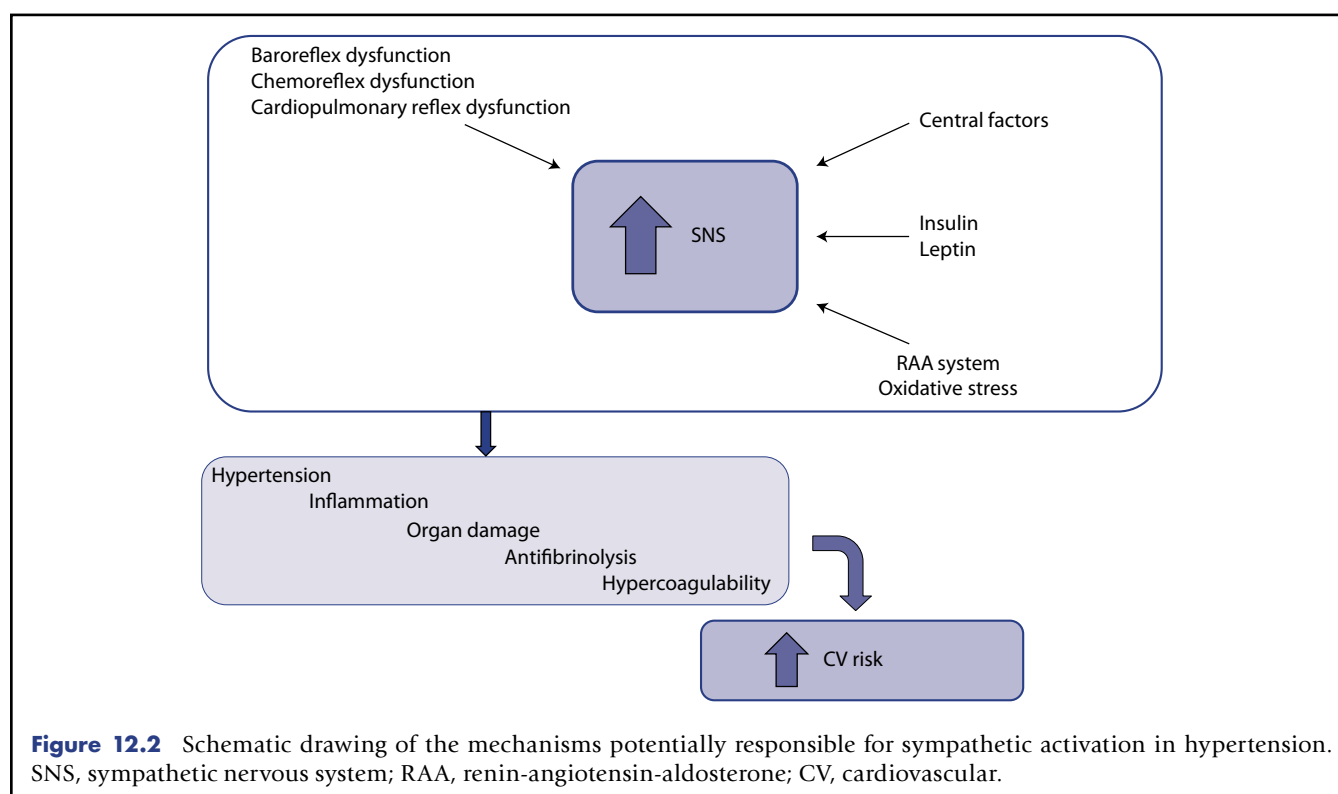
Despite years of investigations on human hypertension, the mechanisms responsible for activation of adrenergic tone are still undefined. Several hypotheses have been advanced (Figure 12.2). The first hypothesis was that the sympathetic overdrive could be dependent by an excessive response to environmental stimuli (i.e. stress, depression, alarm reaction, air pollution, smoke, etc.) inducing a great blood pressure variability and later a more stable and sustained hypertensive state (42). This hypothesis of course cannot be conclusive due to the fact that the definition of real-life stress is difficult, and it is also difficult to standardize and create reproducible laboratory stress to study long-term effects. It has been suggested that a derangement in the sympatho-inhibition by reflexogenic areas that tonically restrain adrenergic outflow may be responsible for the increase in the sympathetic activity (1,2,32). It has been shown in hypertension that arterial baroreflex impairs its ability to control heart rate, but it continues to modulate blood pressure and sympathetic activity (1,13). This observation weakens the baroreflex hypothesis, although it does not completely rule out its possible role in the maintenance and progression of sympathetic drive during increase in the severity of the hypertensive state. This is supported by the evidence that during blood pressure increase there is also an increase in sympathetic modulation exerted by the baroreflex (the so-called resetting phenomenon) that stabilizes the status at the higher values (13). It is also possible to observe that in hypertensive patients with left ventricular hypertrophy or left ventricular dysfunction the

reduced inhibitory influence of cardiac stretch receptors in particular reflexogenic areas, such as the cardiopulmonary receptors and the chemoreceptors, may participate in the occurrence of the hyperadrenergic state (1,2,32).

The hypertensive state is associated with the activation of the renin–angiotensin–aldosterone system. It has been shown that angiotensin II can act centrally to increase adrenergic tone (43). It has also been shown that angiotensin II infusion can increase sympathetic nerve traffic, while angiotensin-converting enzyme inhibitor is able to prevent it (44).

Another factor involved in adrenergic tone control is the hypoxic stimulus. Hypoxia may lead to sympathoexcitation via two mechanisms: augmentation of peripheral chemoreflex sensitivity and direct effects on sites of central regulation. It has been shown that hypoxia increases not only sympathetic activity and blood pressure levels, but also induces an antifibrinolytic activity through an elevation in plasminogen activator inhibition type 1, an oxidative stress through an activation of reduction-oxidation-sensitive gene expression, an inflammatory status with an increase in tumour necrosis factors and interleukins, and hypercoagulability (45–47).

Elevated plasma insulin levels have been demonstrated to increase blood pressure, to alter glucose and lipid metabolism, and to enhance atherogenesis (48). In humans the sympathetic response triggered by insulin is heterogeneous. Acute hyperinsulinemia increases muscle sympathetic nerve activity while renal norepinephrine spillover remains unchanged (49,50). The fact that hypertension is accompanied by high rates of norepinephrine spillover from the kidneys (51) indicates that the increased sympathetic outflow is not confined to the increase in plasma insulin levels (52).



## THERAPEUTIC APPROACH

Based on the key role exerted by adrenergic factors in the development and progression of hypertension and hypertension-related end-organ damage, sympathoinhibition appears to be a key goal of the therapeutic approach. Non-pharmacological lifestyle interventions, such as energy-restricted diet or physical training, have shown to exert not only a control on blood pressure value but also to exert sympathoinhibitory effects through improvement in the baroreflex control. The sympathetic deactivation is paralleled by a clear improvement in insulin sensitivity, a finding that once again shows the close relationships between adrenergic and metabolic function (40,53,54).

Sympathetic deactivation is also one of the goals of pharmacological interventions. Table 12.2 summarizes the information collected with the different antihypertensive drug classes. In the first few days after the administration of an antihypertensive drug it is possible to observe an increase in sympathetic activity due to the reflex activation that follows the unload of arterial baroreceptors (55). Diuretics and short-acting calcium channel blockers induce a sympathetic activation in adrenergic tone, and this is also the case for blockers of  $\alpha$ -adrenergic receptors (56). In contrast, this is not the case for central agents,  $\beta$ -adrenergic receptor blockers, blockers of the renin-angiotensin system, and mineralocorticoid receptor antagonists which are able to reduce the adrenergic tone and improve vagal cardiac control (56,57). However, antihypertensive treatment, although able to reduce blood pressure values, is not able to restore the sympathetic activity to values of subjects with normal blood pressure values. Choice of the drug should take into consideration the possible unfavourable effects of the different compounds. Diuretics and  $\beta$ -blockers have

unfavourable metabolic effects thus inducing a discontinuation. The final effect is a reduced patient's compliance and a negative result on blood pressure control. The new generation of long-acting calcium antagonists and blockers of the renin-angiotensin system appear to be well accepted by patients due to (1) an effective blood pressure control over a 24-h period, (2) neutral or favourable effects on sympathetic function, (3) improvement in insulin sensitivity, and (4) neutral effect on lipid profile (57). Regarding the non-pharmacological antihypertensive approach, two therapeutic procedures have been proposed for the treatment of true resistant hypertension. The first is the implantation of a carotid baroreceptor stimulation device. In a follow-up of 4 years the device has shown to reduce blood pressure values, accompanied by a reduction in the sympathetic tone (58). The second procedure is bilateral renal nerve ablation obtained through catheters delivering high-frequency current or ultrasound. In this case results are not univocal both in control of blood pressure, as reported by a recent randomized trial (59), and on the sympathoinhibitory effects, in which the association between changes in sympathetic activity and changes in blood pressure has been only minor (60,61).

## CONCLUSIONS

Essential hypertension is characterized by an adrenergic activation that appears early in the course of the disease and increases with the severity of the hypertensive state. The adrenergic mechanisms associated with alteration in the mechanisms of autonomic cardiovascular control participate in the development of target-organ damage. Thus, the aim of the therapeutic approach is to reduce this sympathetic activation through non-pharmacological and pharmacological intervention to obtain a good blood pressure control and a reduction in the hypertension-related cardiovascular risk.

**Table 12.2** Effects of non-pharmacological and pharmacological treatment on sympathetic activity

| Intervention           | MSNA |
|------------------------|------|
| Body weight reduction  | ↓    |
| Physical exercise      | ↓    |
| Baroreflex stimulation | ↓    |
| Renal denervation      | ↓, = |
| <b>Drugs</b>           |      |
| Diuretics              | ↑, = |
| Short-acting CCB       | ↑    |
| Long-acting CCB        | =    |
| $\beta$ -blockers      | ↓    |
| ACE-I                  | =, ↓ |
| ARB                    | ↓    |
| Central sympatholytics | ↓    |

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MSNA, muscle sympathetic nerve activity.

## REFERENCES

- Grassi G. Sympathetic neural activity in hypertension and related diseases. *Am J Hypertens* 2010; 23: 1052–1060.
- Grassi G. Assessment of sympathetic cardiovascular drive in human hypertension: Achievements and perspectives. *Hypertension* 2009; 54: 690–697.
- Julius S, Krause L, Schork NJ et al. Hyperkinetic borderline hypertension in Tecumseh, Michigan. *J Hypertens* 1991; 9: 77–84.
- Palatini P, Julius S. The role of cardiac autonomic function in hypertension and cardiovascular disease. *Curr Hypertens Rep* 2009; 11: 199–205.
- Pagani M, Lombardi F, Guzzetti S et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 1986; 59: 178–193.
- Bianchetti MG, Weidmann P, Beretta-Piccoli C et al. Disturbed noradrenergic blood pressure control in normotensive members of hypertensive families. *Br Heart J* 1984; 51: 30–311.
- Ferrier C, Cox H, Esler M. Elevated total body noradrenaline spillover in normotensive members of hypertensive families. *Clin Sci (Lond)* 1993; 84: 225–230.
- Yamada Y, Miyajima E, Tochikubo O et al. Impaired baroreflex changes in muscle sympathetic nerve activity in adolescents who have a family history of essential hypertension. *J Hypertens Suppl* 1988; 6: S525–S528.
- Esler M, Lambert G, Jennings G. Regional norepinephrine turnover in human hypertension. *Clin Exp Hypertens* 1989; 11(suppl 1): 75–89.
- Seravalle G, Lonati L, Buzzzi S et al. Sympathetic nerve traffic and baroreflex function in optimal, normal, and high-normal blood pressure states. *J Hypertens* 2015; 33: 1411–1417.

11. Anderson EA, Sinkey CA, Lawton WJ, Mark AL. Elevated sympathetic nerve activity in borderline hypertensive humans: evidence from direct intraneural recordings. *Hypertension* 1988; 14: 1277–1283.
12. Floras JS, Hara K. Sympathoneural and haemodynamic characteristics of young subjects with mild essential hypertension. *J Hypertens* 1993; 11: 647–655.
13. Grassi G, Cattaneo BM, Seravalle G et al. Baroreflex control of sympathetic nerve activity in essential and secondary hypertension. *Hypertension* 1998; 31: 68–72.
14. Grassi G, Seravalle G, Brambilla G et al. Marked sympathetic activation and baroreflex dysfunction in true resistant hypertension. *Int J Cardiol* 2014; 177: 1020–1025.
15. Grassi G, Seravalle G, Bertinieri G et al. Sympathetic and reflex alterations in systo-diastolic and systolic hypertension of the elderly. *J Hypertens* 2000; 18: 587–593.
16. Brodde OE. Beta-adrenoreceptors in cardiac disease. *Pharmacol Ther* 1993; 60: 405–430.
17. Schobel HP, Fisher T, Heuszer K et al. Preeclampsia - a state of sympathetic overactivity. *N Engl J Med* 1996; 335: 1480–1485.
18. Smith PA, Graham LN, Mackintosh AF et al. Sympathetic neural mechanisms in white-coat hypertension. *J Am Coll Cardiol* 2002; 40: 126–132.
19. Grassi G, Seravalle G, Trevano FQ et al. Neurogenic abnormalities in masked hypertension. *Hypertension* 2007; 50: 537–542.
20. Mancia G, Bombelli M, Sega R, Grassi G. White-coat and masked hypertension. In: Black HR, Elliott WJ (eds) *Hypertension. A Companion to Braunwald's Heart Disease*. Saunders Elsevier, Philadelphia, PA; 2012, 64–68.
21. Grassi G, Seravalle G, Quarti Trevano F et al. Adrenergic, metabolic, and reflex abnormalities in reverse and extreme dipper hypertensives. *Hypertension* 2008; 52: 925–931.
22. Somers VK, Mark AL, Abboud FM. Sympathetic activation by hypoxia and hypercapnia-implications for sleep apnea. *Clin Exp Hypertens* 1988; 10(suppl 1): 413–422.
23. Converse RL Jr, Jacobsen TN, Toto RD et al. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 1992; 327: 1912–1918.
24. Grassi G, Quarti Trevano F, Seravalle G et al. Early sympathetic activation in the initial clinical stages of chronic renal failure. *Hypertension* 2011; 57: 846–851.
25. Schlaich MP, Kaye DM, Lambert E et al. Relation between cardiac sympathetic activity and hypertension-related left ventricular hypertrophy. *Circulation* 2003; 108: 560–565.
26. Grassi G, Seravalle G, Quarti-Trevano F et al. Sympathetic and baroreflex cardiovascular control in hypertension-related left ventricular dysfunction. *Hypertension* 2009; 53: 205–209.
27. Grassi G, Seravalle G, Dell'Oro R et al. Sympathetic and baroreflex function in hypertensive or heart failure patients with ventricular arrhythmias. *J Hypertens* 2004; 22: 1747–1753.
28. Hansson GK. How to chew up cells: lessons for the atherosclerotic plaque. *Circ Res* 2012; 111: 669–671.
29. Mangoni AA, Mircoli L, Giannattasio C et al. Effect of sympathectomy on mechanical properties of common carotid and femoral arteries. *Hypertension* 1997; 30: 1085–1088.
30. Failla M, Grappiolo A, Emanuelli G et al. Sympathetic tone restrains arterial distensibility of healthy and atherosclerotic subjects. *J Hypertens* 1999; 17: 1117–1123.
31. Giannattasio C, Mancia G. Arterial distensibility and the sympathetic nervous system. In: Safar ME, O'Rourke MF (eds) *Handbook of Hypertension, Volume 23. Arterial Stiffness in Hypertension*. Elsevier, Amsterdam; 2006, 213–224.
32. Grassi G, Mark A, Esler M. The sympathetic nervous system alterations in human hypertension. *Circ Res* 2015; 116: 976–990.
33. Cohn JN, Levine TB, Olivari MT et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984; 311: 819–823.
34. Barretto AC, Santos AC, Munhoz R et al. Increased muscle sympathetic nerve activity predicts mortality in heart failure patients. *Int J Cardiol* 2009; 135: 302–307.
35. Florea VG, Cohn JN. The autonomic nervous system and heart failure. *Circ Res* 2014; 114: 1815–1826.
36. Grassi G, Seravalle G, Cattaneo BM et al. Sympathetic activation and loss of reflex sympathetic control in mild congestive heart failure. Grassi G et al. *Circulation* 1995; 92: 3206–3211.
37. Sander D, Winbeck K, Klingelhofer J, Etgen T, Conrad B. Prognostic relevance of pathological sympathetic activation after acute thromboembolic stroke. *Neurology* 2001; 57: 833–838.
38. Zoccali C, Mallamaci F, Parlongo S et al. Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end stage renal disease. *Circulation* 2002; 105: 1354–1359.
39. Andreas S, Haarmann H, Klarner H et al. Increased sympathetic nerve activity in COPD is associated with morbidity and mortality. *Lung* 2014; 192: 235–241.
40. Grassi G, Seravalle G, Brambilla G et al. Regional differences in sympathetic activation in lean and obese normotensive individuals with obstructive sleep apnoea. *J Hypertens* 2014; 32: 383–388.
41. Vaz M, Jennings G, Turner A et al. Regional sympathetic nerve activity and oxygen consumption in obese normotensive human subjects. *Circulation* 1997; 96: 3423–3429.
42. Julius S, Sanchez R, Malayan S et al. Sustained blood pressure elevation to lower body compression in pigs and dogs. *Hypertension* 1982; 4: 782–788.
43. Reid IA. Interactions between ANG II, sympathetic nervous system, and baroreceptor reflexes in regulation of blood pressure. *Am J Physiol Endo Metab* 1992; 262: E763–E778.
44. Miyajima E, Shigemasa T, Yamada Y et al. Angiotensin II blunts, while angiotensin converting enzyme inhibitor augments, reflex sympathetic inhibition in humans. *Clin Exper Pharmacol Physiol* 1999; 26: 797–802.
45. Belaidi E, Joyeux-Faure M, Ribout C et al. Major role for hypoxia inducible factor-1 and the endothelin system in promoting myocardial infarction and hypertension in animal model of obstructive sleep apnea. *J Am Coll Cardiol* 2009; 53: 1309–1317.
46. Guzik TJ, Hoch NE, Brown KA et al. Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. *J Exp Med* 2007; 204: 2449–2460.
47. Bruno RM, Ghiadoni L, Seravalle G et al. Sympathetic regulation of vascular function in health and disease. *Front Physiol* 2012; 3: 28–34.
48. Reaven GM. Banting Lecture. Role of insulin resistance in human disease. *Diabetes* 1988; 37: 1595–1607.
49. Vollenweider P, Tappy L, Randin D et al. Differential effects of hyperinsulinemia and carbohydrate metabolism on sympathetic nerve activity and muscle blood flow in humans. *J Clin Invest* 1993; 92: 147–154.
50. Gudbjornsdottir S, Friberg P, Elam M et al. The effects of metformin and insulin on sympathetic nerve activity, norepinephrine spillover and blood pressure in obese, insulin resistant, normoglycemic, hypertensive men. *Blood Press* 1994; 3: 394–403.
51. Schlaich MP, Lambert E, Kaye DM, Krozowski Z, Campbell DJ, Lambert G, Hastings J, Aggarwal A, Esler MD. Sympathetic augmentation in hypertension: role of nerve firing, norepinephrine uptake, and angiotensin neuromodulation. *Hypertension* 2004; 43: 169–175.
52. Jamerson KA, Julius S, Gudbrandsson T et al. Reflex sympathetic activation induces acute insulin resistance in the human forearm. *Hypertension* 1993; 21: 618–623.
53. Grassi G, Seravalle G, Calhoun DA, Mancia G. Physical training and baroreceptor control of sympathetic nerve activity in humans. *Hypertension* 1994; 23: 294–301.
54. Iwane M, Arita M, Tomimoto S et al. Walking 10,000 steps/day or more reduces blood pressure and sympathetic nerve activity in mild essential hypertension. *Hypertens Res* 2000; 23: 573–580.
55. Grassi G, Seravalle G, Stella ML et al. Sympathoexcitatory responses to the acute blood pressure fall induced by central or peripheral antihypertensive drugs. *Am J Hypertens* 2000; 13: 29–34.
56. Van Zwieten P. Beneficial interactions between pharmacological, pathophysiological and hypertension research. *J Hypertens* 2001; 19: 465–473.
57. Grassi G. Counteracting the sympathetic nervous system in essential hypertension. *Curr Opin Nephrol Hypertens* 2004; 13: 5113–5519.
58. Heusser K, Tank J, Engeli S et al. Carotid baroreceptor stimulation, sympathetic activity, baroreflex function, and blood pressure in hypertensive patients. *Hypertension* 2010; 55: 619–626.
59. Bhatt DL, Kandzari DE, O'Neill WW et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014; 370: 1393–1401.
60. Schmieder RE, Redon J, Grassi G et al. ESH position paper: Renal denervation-an interventional therapy of resistant hypertension. *J Hypertens* 2012; 30: 837–841.
61. Schlaich MP, Schmieder RE, Bakris G et al. International Expert Consensus statement: Percutaneous transluminal denervation for the treatment of resistant hypertension. *J Am Coll Cardiol* 2013; 62: 2031–2045.



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# THE RENIN–ANGIOTENSIN– ALDOSTERONE SYSTEM

# 13

Ulrike M. Steckelings and Thomas Unger

## INTRODUCTION

The renin–angiotensin–aldosterone system (RAAS) is one of the oldest hormonal systems—regardless of whether ‘old’ is defined as phylogenetically old, or in the sense of being discovered a long time ago (1). The first description of a RAAS component came from Robert Tigerstedt and his student Per Bergman as early as 1897, when they injected a kidney homogenate derived from a healthy rabbit into another healthy rabbit, resulting in a marked elevation in blood pressure (BP) in the recipient (2). Tigerstedt and Bergman termed the BP-elevating substance ‘renin’. It took decades until, in 1934, the groups by Eduardo Braun-Menendez in Buenos Aires and by Irvine Page in Indianapolis coincidentally, but independently, found that the actual BP-elevating substance was not renin itself, but a molecule that was cleaved and activated by renin, and which is nowadays termed angiotensin II (Ang II) (3,4).

Today, we know that the RAAS represents a cascade of enzymatic reactions. The huge precursor molecule of Ang II, angiotensinogen, is cleaved by renin, resulting in the still inactive decapeptide angiotensin I (Ang I), which is then further cleaved by the membrane-bound metalloenzyme angiotensin-converting enzyme (ACE) to give the main effector hormone of the RAAS, Ang II (Figure 13.1) (1).

## COMPONENTS OF THE RENIN– ANGIOTENSIN–ALDOSTERONE SYSTEM

### ANGIOTENSINOGEN

Angiotensinogen is a glycosylated  $\alpha_2$ -plasma protein with a molecular weight of 55–65 kDa (5). In situ hybridization studies indicate that the human angiotensinogen gene is located on chromosome 1q42-3. It codes for the angiotensinogen protein, which, in its mature form, is built from 452 amino acids. Renin cleaves the first 10 amino acids, which correspond to Ang I.

There is evidence that a variant of the angiotensinogen gene is associated with increased angiotensinogen plasma levels and hypertension (5).

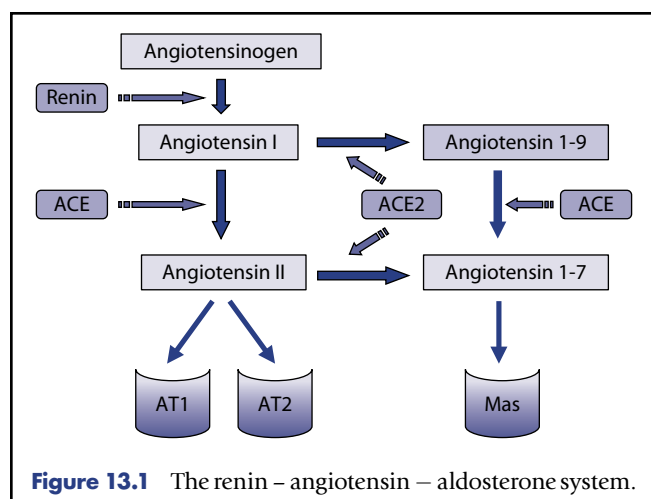
### RENIN

The gene encoding the renin precursor preprorenin is localized on chromosome 1q32. Mature renin contains 340 amino acids and has a mass of 37 kD (6). Renin is primarily released by the juxtaglomerular apparatus of the kidney. Renin secretion is under tight control of several parameters, such as BP and blood volume, plasma sodium content, and sympathetic activation (7). A tight control of renin release is absolutely necessary, because cleavage of angiotensinogen by renin is the rate-limiting step in the enzymatic cascade leading to Ang II synthesis, i.e. the rate of angiotensinogen cleavage is set by the amount and activity of renin, not by the amount of angiotensinogen, which is always available in abundance in the plasma.

### ANGIOTENSIN-CONVERTING ENZYME

The gene for ACE has been mapped to chromosome 17q23 and translates into a 150 kDa protein, which belongs to the family of zinc metallopeptidases (8). ACE cleaves the C-terminal dipeptide His-Leu from Ang I, thus generating Ang II. However, Ang I is by far not the only substrate of ACE. ACE also metabolizes bradykinin, substance P, luteinizing hormone (LH)-releasing hormone, enkephalins, or the insulin  $\beta$ -chain. In all these latter cases, cleavage by ACE does not elicit an activation of the molecule (as with Ang I), but degradation and inactivation. Thus, inhibition of ACE activity, which is one of the most common pharmacological principles in cardiovascular medicine, not only leads to a decrease in Ang II synthesis, but also to the accumulation of those molecules, which are physiologically degraded by ACE.

A variation in the ACE gene structure was recognized in 1990, consisting of the insertion (I) or deletion (D) of a 250 BP DNA fragment located in intron 16 (9). This so-called ‘ACE I/D polymorphism’ has been suspected to be associated with a variety of cardiovascular and noncardiovascular diseases but currently, conclusive data pointing to an association with the I/D polymorphism only exist for diabetic nephropathy and Alzheimer’s disease, while reports on most cardiovascular phenotypes are still controversial



(10). In recent years, a number of additional ACE polymorphisms have been identified whose functional significance still needs to be clarified.

### ANGIOTENSIN-CONVERTING ENZYME 2 (ACE2)

In 2000, the first known homolog of ACE, ACE2, was cloned (11,12). ACE2 catalyzes the generation of Ang 1-9 from Ang I and of Ang 1-7 from Ang II (Figure 13.1). It is insensitive to ACE inhibitors. The fact that ACE2 metabolizes Ang II to give the vasodilator Ang 1-7 has been interpreted to mean that ACE2 provides a counterbalance, preventing the deleterious consequences of overactivity of the classic RAAS (13).

Interestingly, ACE2 has recently been identified to be a receptor for the SARS virus (14).

### ANGIOTENSIN 1-7

Ang 1-7 is cleaved from Ang I by various endopeptidases and from Ang II by ACE2 (15). According to current knowledge there is a specific receptor for Ang 1-7 termed Mas, which mediates actions of Ang 1-7 in physiological concentrations (16). These actions comprise growth inhibition of vascular cells and inhibition of renal tubular  $\text{Na}^+\text{-K}^+\text{-ATPase}$ , thus facilitating natriuresis and diuresis, protection from ischemia/reperfusion injury, antiarrhythmic features, inhibition of oxidative stress, and anti-inflammation. Ang 1-7 in pharmacological and suprapharmacological concentrations may also bind to the AT2R and even the AT1R (17). A recent publication in fact suggested that Ang 1-7 acts as an endogenous  $\beta$ -arrestin recruiting-biased agonist at the AT1R, which mediates cardioprotection (18). It further seems that for exerting some of its actions, Ang 1-7 depends on dimerization of its receptor MAS with the AT2R (19).

### ROLE OF RENIN AND ACE BEYOND THE CLASSICAL RAAS CASCADE

In recent years, it has become clear that the enzymes required for Ang II synthesis, renin and ACE, serve not

only to generate Ang II, but additionally act as ligands or receptors, respectively.

In 1996 and continued in 2002, a membrane receptor was reported which binds renin and prorenin (20,21). Upon binding of renin/prorenin, this so-called (pro-)renin receptor [(P)RR] reacts in two ways: a) an increase in enzymatic activity of both renin and prorenin resulting in enhanced production of Ang I/Ang II, and b) activation of signalling cascades in an Ang II-independent way, which includes nuclear translocation of the transcription factor promyelocytic leukaemia zinc finger (PLZF) and phosphorylation of the mitogen-activated protein (MAP) kinases ERK1 and ERK2 (21,22). The (patho-)physiological relevance and consequences of (pro)renin binding to the (P)RR are still not completely elucidated, and data are controversial (23). Recent evidence rather suggests that the primary role of the (P)RR is RAAS independent but involves a role in the canonical and noncanonical Wnt signalling pathways as well as V-ATPase dependent intracellular vesicle trafficking, vesicular acidification and autophagy (23).

ACE can act as a receptor itself in that the intracellular tail is phosphorylated upon binding of ACE inhibitors and bradykinin (but not Ang I) (24). Ligand binding increases the activity of ACE-associated c-Jun N-terminal kinase (JNK) and elicits the accumulation of phosphorylated c-Jun in the nucleus.

### CIRCULATING AND LOCAL RAAS

Originally, the RAAS has been described as a circulating endocrine system, with angiotensinogen being released by the liver, and renin secreted from the juxtaglomerular apparatus of the kidney, both 'joining' in the circulation for processing of Ang I (25). Ang I then circulates through the body's vasculature, getting almost continuously exposed to and cleaved by ACE, which is predominantly localized on the membranes of vascular endothelial cells. Thus, Ang II is generated within the blood and distributed throughout the body, thereby enabling systemic effects such as vasoconstriction or aldosterone release. The main purpose of these systemic effects is to raise BP and minimize loss of body fluids. They represent the body's 'emergency kit' in case of a sudden fall in BP, for example, due to massive bleeding or shock from any cause.

Many years after the detection and characterization of the systemic RAAS, in the early 1990s, the novel concept of so-called local RAASs arose (26). In the meantime, the expression of all RAAS components could be demonstrated in a broad variety of tissues, indicating local Ang II synthesis. Some of these tissues belong to the cardiovascular system and are involved in 'classical' Ang II actions; these are essentially the blood vessels, the kidney, and the heart. However, a complete local RAAS has also been detected in various 'unexpected' locations, for example, in organs which are not regarded as being part of the cardiovascular system, among them the central and peripheral nervous tissue, adipose tissue, digestive organs (pancreas, stomach, gut), skin and reproductive organs.

### ANGIOTENSIN RECEPTORS

Ang II exerts its actions primarily via two receptor subtypes termed AT1 and AT2 (1). The existence of more

than just one Ang II receptor had long been suspected but was only proven in 1989 owing to the development of ligands specific for the AT<sub>1</sub>- or AT<sub>2</sub>-receptor, respectively. By the time these receptor subtypes were identified, the scientific community thought of Ang II as a purely cardiovascular hormone responsible for BP regulation as well as volume and electrolyte homeostasis. However, it turned out that all of the well-known cardiovascular actions of Ang II (e.g. vasoconstriction, vasopressin release, Na- and water reabsorption directly and by aldosterone release) could be attributed to the AT<sub>1</sub>R, leaving the AT<sub>2</sub>R's physiological role and signalling an enigma over many years. Only much later, evidence accumulated showing that the AT<sub>2</sub>R in many aspects opposes AT<sub>1</sub>R-mediated actions (27). Whether this 'ying-yang' relationship between AT<sub>1</sub>R and AT<sub>2</sub>R plays an important role for BP regulation has not yet been decided and may be restricted to certain vascular beds or only occur under pathological conditions such as hypertension (28). However, the counterplay between the two receptor subtypes definitely seems important in the context of 'new' Ang II actions, which have only been detected in recent years and which comprise, for example, the modulation of cell proliferation, fibrosis and inflammation (27).

## AT<sub>1</sub> RECEPTOR

The genetic message for the human AT<sub>1</sub> receptor is located on chromosome 3q22 encoding a 359 amino acid protein (1). In contrast to humans, rodents possess two different AT<sub>1</sub>-receptors, termed AT<sub>1A</sub> and AT<sub>1B</sub>, with the AT<sub>1A</sub> receptor predominating in most tissues. The AT<sub>1</sub>R belongs to the family of G-protein–coupled receptors displaying seven transmembrane domains. It is coupled to a great variety of signalling pathways including activation of phospholipase A, C or D, generation of inositolphosphates, opening of calcium channels or the activation of diverse serine/threonine- and tyrosine-kinases (1).

## AT<sub>2</sub> RECEPTOR

The AT<sub>2</sub>R gene is located on the X chromosome and was mapped to the Xq22-q23 region. It is built from three exons, but the region encoding the AT<sub>2</sub>R protein (a 363 amino acids molecule) is exclusively located on exon 3 (1). Like the AT<sub>1</sub>R, the AT<sub>2</sub>R also represents a receptor with seven-transmembrane domains (29). However, as revealed very recently by crystallization of the receptor, in the activated state G-protein and  $\beta$ -arrestin binding is prevented by a conformational change that causes the intracellular helix VIII to change orientation and cover the binding sites of G-proteins and  $\beta$ -arrestin at the receptor (30). This novel finding supports the proposition that the functionally relevant signalling mechanisms of the AT<sub>2</sub>R are unconventional and include, for example, specific binding proteins (ATIP, PLZF), activation of various phosphatases, activation of the cGMP/nitric oxide (NO) system and stimulation of phospholipase A<sub>2</sub> (31–33). Human AT<sub>1</sub>R and AT<sub>2</sub>R share only 34% homology, and they differ profoundly with respect to tissue distribution, signalling and functions.

## LOCALIZATION OF ANGIOTENSIN RECEPTORS

Localization and proportion of AT<sub>1</sub>R and AT<sub>2</sub>R undergo profound changes in the course of development from early gestation to adulthood. While the AT<sub>2</sub>R predominates in embryonic and fetal tissues, the AT<sub>1</sub>R/AT<sub>2</sub>R ratio changes dramatically after birth in favour of the AT<sub>1</sub>R (27). Consequently, in the adult organism, the AT<sub>1</sub>-receptor is abundantly expressed in most tissues, while the AT<sub>2</sub>R is restricted to certain locations or only expressed at levels close to the detection level. Remarkably, in the case of tissue injury or remodelling, AT<sub>2</sub>R expression is strongly increased. In the *heart*, AT<sub>1</sub>R and AT<sub>2</sub>R are localized on cardiomyocytes, while normal cardiac fibroblasts appear to possess AT<sub>1</sub>R only, but have the ability to recruit AT<sub>2</sub>R in case of a pathological condition, for example, myocardial infarction or congestive heart failure (1,26). In the *blood vessel wall*, all major cell types, vascular smooth muscle cells, endothelial cells and fibroblasts express both AT<sub>1</sub>- and AT<sub>2</sub>-receptors (1,26). In the *kidney*, the main structures of AT<sub>1</sub>R expression comprise the interlobular arteries and the surrounding fibrous tissue, the glomeruli and the cortical tubules, while the AT<sub>2</sub>R is found in large preglomerular vessels and in the interstitium (1,26). Angiotensin receptor expression in the *brain* varies substantially between certain nuclei, but both receptors are found in cardiovascular control centres. Very recently, the development of an AT<sub>2</sub>R report mouse strain has shed greater light on the localization of AT<sub>2</sub>R in the CNS (34). Since the cerebral expression pattern of AT<sub>1</sub>R and AT<sub>2</sub>R is very complex, the reader is referred to review articles addressing this topic (35,36). For various structures of the *peripheral nervous system*, such as ganglia, the vagus nerve, intracardiac conduction systems, enteric nerves or pre-synaptic membranes of various locations, the presence of AT<sub>1</sub>R has been demonstrated. In contrast, AT<sub>2</sub>R expression in peripheral nerves is only rarely described and seems to be weak or nonexistent (1,26). However, there is strong evidence for an upregulation and functional role of AT<sub>2</sub>R in neuronal regeneration in the peripheral and central nervous system (37–39). In *adrenals*, the AT<sub>1</sub>R is primarily found in the zona glomerulosa, while the AT<sub>2</sub>R is preferentially located in the medulla (40). Both angiotensin receptors are also present in *female and male reproductive organs*, such as the uterus, fallopian tubes, epididymis, testes and mature or immature spermatogenic cells (1,26). The uterus represents one of the very few organs in which the AT<sub>2</sub>R is expressed in much higher density than the AT<sub>1</sub>R. During pregnancy, AT<sub>2</sub>R density decreases by more than 90%. Coincidentally, AT<sub>1</sub>R density increases progressively in the trophoblast and placental vasculature with gestational age. In testes, epididymis and sperm, the AT<sub>1</sub>R is the dominating receptor or the only subtype described. Various cells and structures of human *skin* are targets of Ang II actions via both AT<sub>1</sub>R and AT<sub>2</sub>R, namely keratinocytes, dermal fibroblasts, dermal microvascular endothelial cells, hair follicles and sebaceous glands, with the AT<sub>1</sub>R predominating in all of these locations in healthy skin (41). Most organs of the *digestive tract* also host AT<sub>1</sub>R and AT<sub>2</sub>R, among them salivary glands, intestine, and pancreas. In both *white and brown adipose tissue*, the AT<sub>1</sub>R is present most abundantly. Interestingly, angiotensin receptors have also been demonstrated on *white blood cells* (mononuclear leukocytes, macrophages), which can act as

a kind of 'mobile' RAAS, accumulating at places of injury and inflammation (42).

Other organs displaying AT1R and AT2R comprise the lung, retina, spleen, thymus and liver (1).

## PHYSIOLOGICAL ACTIONS OF ANGIOTENSIN II

Since angiotensin receptors mediate a wide variety of actions depending on receptor subtype, tissue or species, we concentrate in this chapter on their cardiovascular actions in health and disease, with an emphasis on hypertension.

One of the major physiological functions of Ang II consists in the control and maintenance of adequate BP. This is achieved by a row of independent mechanisms, one of them the control of vascular tone.

Vascular tone is determined by a well-orchestrated action of endothelial cells and vascular smooth muscle cells (VSMCs). In this context, stimulation of the AT1R on VSMCs is responsible for the contractile response via activation of phospholipase C and an increase in intracellular Ca-concentrations (43). Endothelial cells are capable of promoting vasodilation by synthesis of NO, which can penetrate into VSMC, where it initiates cGMP generation, thus stimulating protein kinase G, which again leads to a decrease in cytoplasmic calcium. Apart from its direct effect on vascular tone, Ang II also promotes vasoconstriction by facilitating noradrenalin release from vascular nerve endings and by improving the responsiveness of VSMC to noradrenalin (44).

Ang II, via the AT2R, has been shown to induce NO synthesis by activation of eNOS through phosphorylation of the serine1177 residue and dephosphorylation of tyrosine657 (45,46). There is strong evidence that the AT2R-induced synthesis and release of NO translates into vasodilation in isolated vessels *ex vivo* (47). However, with the exception of specific conditions such as intracerebroventricular or intrarenal application of AT2R agonists or obese animals, AT2R stimulation does not lead to a lowering of systemic blood pressure in animals.

Apart from the above-described effect of Ang II on BP by modification of the diameter of resistance arteries, control and maintenance of adequate BP by Ang II furthermore involves the modulation of extracellular fluid volume. Ang II plays a major role in volume and electrolyte homeostasis by its numerous actions on kidney function. For example, Ang II can directly modify the glomerular filtration rate by constricting efferent and afferent arterioles (48). In addition, Ang II is able to facilitate sodium retention by direct effects in the proximal tubule or by indirect effects such as decreased medullary blood flow or an enhanced filtration fraction. Ang II-induced aldosterone release from the adrenals represents another mechanism contributing to the control of sodium and water retention. All these renal effects resulting in sodium and water reabsorption are mediated via the AT1R (1,26,48). In recent years, much progress has been made in the understanding of the role of the AT2R in water and sodium homeostasis. There is evidence that AT2R stimulation may inhibit renin release from the juxtaglomerular apparatus, thus acting in concert with the AT1R, which is a very rare exception of the rule that the AT2R counteracts AT1R actions (49). Furthermore, recent data point to

a natriuretic effect of the AT2R through internalisation/inactivation of the Na<sup>+</sup>/H<sup>+</sup> exchanger-3 and Na<sup>+</sup>/K<sup>+</sup> ATPase within the proximal tubule (50). The natriuretic effect is of such strength that the AT2R may be regarded as potential target for novel diuretics.

The central actions of Ang II affecting blood pressure control are also subject to the ying-yang relationship between AT1R and AT2R: while the AT1R promotes vasopressin release and sympathetic tone, the AT2R inhibits vasopressin release and sympathetic outflow by interference with GABAergic signalling (51,52).

## PATHOPHYSIOLOGICAL ACTIONS OF ANGIOTENSIN II IN HYPERTENSION AND RELATED END-ORGAN DAMAGE

While the above-stated actions of Ang II on blood vessels, kidneys and the brain serve to maintain adequate BP and extracellular fluid volume in times of sodium depletion (a problem our early ancestors were confronted with more than present-day populations) or fluid (blood) loss, an excess of circulating or local Ang II or an overactivity of the RAAS have deleterious effects and contribute to hypertension and related end-organ damage.

For some forms of secondary hypertension, the activation of the RAAS is an obvious and well-examined pathophysiological mechanism (53). For instance, in the case of reduced renal perfusion pressure as a result of renal artery stenosis or parenchymal disease (e.g. chronic glomerulonephritis or pyelonephritis, polycystic renal disease, connective tissue disorders), renin secretion from the juxtaglomerular apparatus is increased, resulting in elevated plasma Ang II levels (7). The pathophysiological role of the RAAS in essential hypertension is less obvious. The most prominent hint towards a dysregulation of the RAAS in essential hypertension comes from the observation that in the majority of hypertensive patients, renin levels are either normal or upregulated, although reduced renin levels would be expected as a reaction to increased renal perfusion pressure. Only about one-third of patients display low renin levels (54). Several suggestions have been made to explain what causes these 'inappropriately' high levels of renin: (a) increased sympathetic drive, (b) nephron heterogeneity with a subpopulation of ischaemic nephrons responsible for increased tonic renin release and (c) defective feedback regulation of RAAS activity in kidneys and adrenals in response to varying levels of sodium intake.

Hypertension is one of the most relevant risk factors for cardiovascular morbidity and mortality due to its deleterious effects on end-organ structure and function (55). It is well established for most affected tissues that an activated RAAS contributes to hypertension-related end-organ damage (56). The vasculature reacts to chronically elevated BP levels with remodelling of the vascular wall, leading to an increased media-to-lumen ratio. This growth-promoting effect of Ang II can be largely attributed to the activation of growth factors such as PDGF, VEGF or bFGF via the AT1R (55). However, there is more to vascular end-organ damage than just hypertrophy. Ang II via the AT1-receptor stimulates NAD(P)H oxidases, resulting in the production of reactive oxygen species (ROS) and



increased oxidative stress (57). NO, a major vasodilator and vasoprotective agent, reacts strongly with the superoxide anion  $O_2^-$ , thus losing bioactivity (58). Furthermore, the powerful oxidant  $ONOO^-$  emanates from this reaction. Oxidative stress and ROS production are nowadays considered to be stimuli for local inflammation and fibrosis via activation of key transcription factors, such as NF-kappaB and AP-1, followed by an enhanced transcriptional rate of various cytokines, chemokines, adhesion factors and, again, growth factors (59). Direct stimulation of NF-kappaB and AP-1 by Ang II itself may further add to this effect (60). While the arising inflammatory response contributes to the higher susceptibility of hypertensive patients for developing atherosclerosis and cardiovascular disease, vascular fibrosis is the major determinant of arterial stiffness.

In contrast to the role of the AT1R in hypertensive vascular remodelling, inflammation and atherogenesis, the AT2R has been described to attenuate hypertension-induced vascular remodelling, inflammation and to delay the development of atherosclerosis (61–63).

Regarding Ang II actions in the heart, it is well documented that Ang II via the AT1R promotes cardiac hypertrophy, which is mainly due to cardiomyocyte hypertrophy (64). Cardiac hypertrophy develops as a reaction to chronically elevated intracardiac pressure (due to hypertension or as a result of stenosis of the cardiac valves or the big, afferent blood vessels). Cardiac hypertrophy is a compensatory mechanism, which in earlier stages preserves cardiac function. However, an excess of hypertrophy leads to decompensation, resulting in cardiac failure and increased mortality (65). Several mechanisms lead to a deterioration of cardiac function due to enhanced Ang II production, among them impaired diastolic calcium handling (66), cardiac fibrosis (67), impaired diastolic relaxation due to disturbed sarcoplasmic reticulum calcium pump activity (68) and also arrhythmias (69).

The role of the AT2R in cardiac hypertrophy – whether it is pro- or antihypertrophic – is a current matter of debate. Controversial data arose from studies in AT2R-knockout mice with different locations of the deletion and with different genetic backgrounds. However, more recent studies using AT2R-agonists for direct AT2R-stimulation rather pointed to an antihypertrophic or neutral role of the AT2R regarding cardiac hypertrophy (70,71).

Renal damage is a frequent long-term consequence of hypertension (72). It is characterized by renal arteriolar thickening, fibrinoid deposition into the glomeruli, and is accompanied by an inflammatory response and proteinuria (73). Ang II by acting on the AT1R is involved in these pathogenetic mechanisms by its growth-promoting, proinflammatory and profibrotic features as discussed above. Furthermore, fibrinoid deposition is facilitated by leakage of renal microvessels (74). Ang II seems to promote leakage of microvessels in the kidney and other organs (e.g. in retina or heart) via increased VEGF expression (75).

In contrast, the protective effect of AT2R stimulation on hypertensive kidney damage has been demonstrated in spontaneously hypertensive rats and in Ang II induced hypertension (50,76,77).

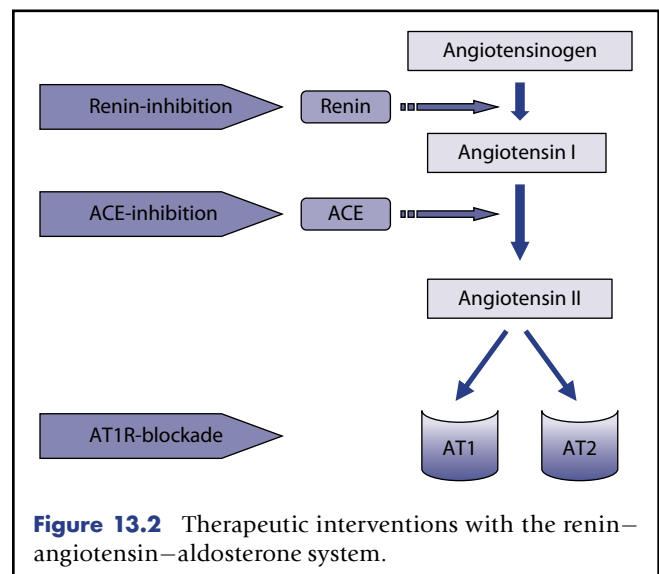
Hypertension is the most important risk factor for stroke. Stroke is caused by either intracranial haemorrhage or cerebral infarction, the latter being a consequence of atherosclerotic plaque formation in arteries nourishing the brain or of embolism of cardiac origin (78). Ang II contributes to

ischaemic cerebral damage by promoting oxidative stress and inflammation, by further deteriorating brain perfusion and by pro-apoptotic mechanisms (79).

Again, the AT2R has effects opposing those of the AT1R and acts neuroprotective in stroke by various mechanisms including anti-inflammation and BDNF synthesis (80).

## THERAPEUTIC INTERVENTION WITH THE RAAS

Therapeutic intervention with the RAAS is discussed in detail in the following chapters of this book. In brief, there are two main mechanisms by which the RAAS can be inhibited: either by inactivation of the enzymes responsible for Ang II generation or by blockade of the angiotensin AT1-receptor (Figure 13.2) (81). ACE inhibitors have been the first development in this row of RAAS-interfering drugs (82). Originally, they were thought of as therapeutics for hypertensive patients with an activated RAAS and high renin plasma levels. However, it soon turned out that they were also effective in patients with normal renin plasma activity, which constitute the majority of patients with essential hypertension. Moreover, in parallel with growing scientific knowledge about Ang II actions beyond BP regulation, in particular its role in the promotion of end-organ damage, clinical data revealed that ACE inhibitors have the potential to prevent end-organ damage by mechanisms exceeding the reduction of BP, for example, by inhibition of inflammation, fibrosis or hypertrophy (83). The same additional effectiveness was found to be a feature of AT1R-blockers (ARBs) (83). Both drugs – ACE inhibitors and ARBs – act by diminishing Ang II actions mediated by the AT1 receptor – ACE inhibitors by reducing the amount of stimulating Ang II, ARBs by direct receptor blockade. Furthermore, both drugs display additional mechanisms of action: ACE inhibitors by accumulation of bradykinin, thus stimulating bradykinin actions such as increased NO synthesis, and also by enhancing the formation of the protective RAAS mediator, angiotensin-(1-7), and ARBs by facilitating the activation of unblocked AT2-receptors by Ang II.





In 2007, aliskiren was approved as first-in-class direct renin inhibitor, thus introducing a new method of pharmacological interference with the RAAS into the clinics (84). Aliskiren, which inhibits the RAAS cascade at its initial, rate-limiting enzymatic step, was hoped to have superior BP-lowering properties, being effective also in resistant hypertension. These hopes were not fulfilled. Instead, when combined with standard therapy, including other RAAS-interfering drugs in patients with type 2 diabetes, aliskiren treatment led to an increased number of adverse effects such as hyperkalaemia and hypotension (85).

The latest developments focus mainly on fixed-dose combinations of ACE inhibitors or ARBs with other approved antihypertensives such as diuretics or calcium channel blockers. However, the combination of two RAAS-interfering drugs seems to elicit more problems than benefits, especially in patients with renal dysfunction (86).

Angiotensin-neprilysin inhibitors (ARNIs) are a recently approved, novel drug class (87). Their mechanism of action combines AT1R antagonism with inhibition of degradation of natriuretic peptides by neprilysin, thus taking advantage of the natriuretic and vasodilatory actions of the natriuretic peptides. Although ARNIs were initially developed and approved for the treatment of heart failure, various clinical studies suggest that they may also be useful as a novel class of antihypertensives (88).

Last but not least, there is a current renaissance of the aldosterone antagonists spironolactone and the more recently developed eplerenone, the latter having higher specificity for the mineralocorticoid receptor, resulting in fewer side effects (89,90). Two recent large clinical studies provided evidence that both drugs are capable of reducing mortality in heart failure patients (60,61).

Taken together, the RAAS is one of the major determinants in the pathogenesis of hypertension and related organ damage. Consequently, several current and future therapeutic approaches aim to inhibit the synthesis of the main effector hormone, Ang II, or they prevent the stimulation of AT1R. However, the RAAS also harbours its own opponents, which in many cases apparently counteract the detrimental actions mediated via the AT1R – the main opponents being the AT2-receptor, ACE2 and Ang 1-7. Whether stimulation of this integrated counteracting system may be a novel therapeutic option will have to be clarified by respective drug development programs in the future (91).

## REFERENCES

- de Gasparo M, Catt KJ, Inagami T et al. International union of pharmacology. XXIII. The angiotensin II receptors. *Pharmacol Rev* 2000; 52(3): 415–472.
- Tigerstedt R, Bergmann P. Niere und Kreislauf. *Skand Arch Physiol* 1898; (8): 223–271.
- Page IH, Helmer OM. A crystalline pressor substance (angiotonin) resulting from the reaction between renin and renin-activator. *J Exp Med* 1940; 71(1): 29–42.
- Braun-Menendez E, Fasciolo JC, Leloir LF, Muñoz JM. The substance causing renal hypertension. *J Physiol (Lond)* 1940; 98(3): 283–298.
- Corvol P, Jeunemaitre X. Molecular genetics of human hypertension: Role of angiotensinogen. *Endocr Rev* 1997; 18(5): 662–677.
- Kaschina E, Steckelings UM, Unger T. Renin and hypertension. In: Martini L (ed) *Encyclopedia of Endocrine Disease*. Boston: Elsevier; 2004: S609–S614.
- Friis UG, Madsen K, Stubbe J et al. Regulation of renin secretion by renal juxtaglomerular cells. *Pflügers Arch* 2013; 465(1): 25–37.
- Jaspard E, Costerousse O, Wei L et al. The angiotensin I-converting enzyme (kininase II): Molecular and regulatory aspects. *Agents Actions Suppl* 1992; 38(Pt 1): 349–358.
- Rigat B, Hubert C, Alhenc-Gelas F et al. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *J Clin Invest* 1990; 86(4): 1343–1346.
- Sayed-Tabatabaei FA, Oostra BA, Isaacs A et al. ACE polymorphisms. *Circ Res* 2006; 98(9): 1123–1133.
- Tipnis SR, Hooper NM, Hyde R et al. A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. *J Biol Chem* 2000; 275(43): 33238–33243.
- Donoghue M, Hsieh F, Baronas E et al. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Circ Res* 2000; 87(5): E1–E9.
- Danilczyk U, Penninger JM. Angiotensin-converting enzyme II in the heart and the kidney. *Circ Res* 2006; 98(4): 463–471.
- Li W, Moore MJ, Vasilieva N et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003; 426(6965): 450–454.
- Passos-Silva DG, Verano-Braga T, Santos RAS. Angiotensin-(1-7): Beyond the cardio-renal actions. *Clin Sci* 2013; 124(7): 443–456.
- Santos RAS, Simoes e Silva AC, Maric C et al. Angiotensin-(1-7) is an endogenous ligand for the G protein-coupled receptor Mas. *Proc Natl Acad Sci USA* 2003; 100(14): 8258–8263.
- Bosnyak S, Jones ES, Christopoulos A et al. Relative affinity of angiotensin peptides and novel ligands at AT1 and AT2 receptors. *Clin Sci* 2011; 121(7): 297–303.
- Teixeira LB, Parreiras-E-Silva LT, Bruder-Nascimento T et al. Ang-(1-7) is an endogenous  $\beta$ -arrestin-biased agonist of the AT1 receptor with protective action in cardiac hypertrophy. *Sci Rep* 2017; 7(1): 11903.
- Leonhardt J, Villela DC, Teichmann A et al. Evidence for heterodimerization and functional interaction of the angiotensin type 2 receptor and the receptor MAS. *Hypertension* 2017; 69(6): 1128–1135.
- Nguyen G, Delarue F, Berrou J et al. Specific receptor binding of renin on human mesangial cells in culture increases plasminogen activator inhibitor-1 antigen. *Kidney Int* 1996; 50(6): 1897–1903.
- Nguyen G, Delarue F, Burcklé C et al. Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *J Clin Invest* 2002; 109(11): 1417–1427.
- Schefe JH, Menk M, Reinemund J et al. A novel signal transduction cascade involving direct physical interaction of the renin/prorenin receptor with the transcription factor promyelocytic zinc finger protein. *Circ Res* 2006; 99(12): 1355–1366.
- Sihn G, Burckle C, Rousselle A et al. (Pro)renin receptor: Subcellular localizations and functions. *Front Biosci (Elite Ed)* 2013; 5: 500–508.
- Kohlstedt K, Brandes RP, Müller-Esterl W et al. Angiotensin-converting enzyme is involved in outside-in signaling in endothelial cells. *Circ Res* 2004; 94(1): 60–67.
- Hall JE. Historical perspective of the renin-angiotensin system. *Mol Biotechnol* 2003; 24(1): 27–39.
- Paul M, Poyan Mehr A, Kreutz R. Physiology of local renin-angiotensin systems. *Physiol Rev* 2006; 86(3): 747–803.
- Steckelings UM, Kaschina E, Unger T. The AT2 receptor—a matter of love and hate. *Peptides* 2005; 26(8): 1401–1409.
- Duke LM, Evans RG, Widdop RE. AT2 receptors contribute to acute blood pressure-lowering and vasodilator effects of AT1 receptor antagonism in conscious normotensive but not hypertensive rats. *Am J Physiol Heart Circ Physiol* 2005; 288(5): H2289–H2297.
- Hansen JL, Servant G, Baranski TJ et al. Functional reconstitution of the angiotensin II type 2 receptor and G(i) activation. *Circ Res* 2000; 87(9): 753–759.
- Zhang H, Han GW, Batyuk A et al. Structural basis for selectivity and diversity in angiotensin II receptors. *Nature* 2017; 544(7650): 327–332.
- Wruck CJ, Funke-Kaiser H, Pufe T et al. Regulation of transport of the angiotensin AT2 receptor by a novel membrane-associated Golgi protein. *Arterioscler Thromb Vasc Biol* 2005; 25(1): 57–64.
- Nouet S, Amzallag N, Li J-M et al. Trans-inactivation of receptor tyrosine kinases by novel angiotensin II AT2 receptor-interacting protein, ATIP. *J Biol Chem* 2004; 279(28): 28989–28997.
- Unger T, Steckelings UM, Santos RAS dos, Herausgeber. The protective arm of the renin angiotensin system (RAS). In: *The Protective Arm of the Renin Angiotensin System (RAS)* [Internet]. Boston: Academic Press; 2015 [zitiert 14. September 2017]. S. i–ii. Verfügbar unter: <http://www.sciencedirect.com/science/article/pii/B9780128013649099892>.

34. de Kloet AD, Wang L, Ludin JA et al. Reporter mouse strain provides a novel look at angiotensin type-2 receptor distribution in the central nervous system. *Brain Struct Funct* 2016; 221(2): 891–912.
35. McKinley MJ, Albiston AL, Allen AM et al. The brain renin-angiotensin system: Location and physiological roles. *Int J Biochem Cell Biol* 2003; 35(6): 901–918.
36. Steckelings UM, Bottari SP, Unger T. Angiotensin receptor subtypes in the brain. *Trends Pharmacol Sci* 1992; 13(9): 365–368.
37. Gallinat S, Yu M, Dorst A et al. Sciatic nerve transection evokes lasting up-regulation of angiotensin AT2 and AT1 receptor mRNA in adult rat dorsal root ganglia and sciatic nerves. *Brain Res Mol Brain Res* 1998; 57(1): 111–122.
38. Reinecke K, Lucius R, Reinecke A et al. Angiotensin II accelerates functional recovery in the rat sciatic nerve in vivo: Role of the AT2 receptor and the transcription factor NF-kappaB. *FASEB J* 2003; 17(14): 2094–2096.
39. Lucius R, Gallinat S, Rosenstiel P et al. The angiotensin II type 2 (AT2) receptor promotes axonal regeneration in the optic nerve of adult rats. *J Exp Med* 1998; 188(4): 661–670.
40. Allen AM, Zhuo J, Mendelsohn FA. Localization of angiotensin AT1 and AT2 receptors. *J Am Soc Nephrol* 1999; 10(Suppl 11): S23–S29.
41. Steckelings UM, Wollschläger T, Peters J et al. Human skin: Source of and target organ for angiotensin II. *Exp Dermatol* 2004; 13(3): 148–154.
42. Jurewicz M, McDermott DH, Sechler JM et al. Human T and natural killer cells possess a functional renin-angiotensin system: Further mechanisms of angiotensin II-induced inflammation. *J Am Soc Nephrol* 2007; 18(4): 1093–1102.
43. Touyz RM, Schiffrin EL. Signal transduction mechanisms mediating the physiological and pathophysiological actions of angiotensin II in vascular smooth muscle cells. *Pharmacol Rev* 2000; 52(4): 639–672.
44. Lohmeier TE, Reinhart GA, Mizelle HL et al. Influence of the renal nerves on sodium excretion during progressive reductions in cardiac output. *Am J Physiol* 1995; 269(3 Pt 2): R678–R690.
45. Yayama K, Hiyoshi H, Imazu D, Okamoto H. Angiotensin II stimulates endothelial NO synthase phosphorylation in thoracic aorta of mice with abdominal aortic banding via type 2 receptor. *Hypertension* 2006; 48(5): 958–964.
46. Peluso A, Bertelsen J, Andersen K et al. [PS 01-28] AT2-receptor stimulation promotes no release through enos serine 1177 phosphorylation and enos tyrosine 657 dephosphorylation. *J Hypertens* 2016; 34: e103.
47. Carey RM, Park J. Role of angiotensin type 2 receptors in vasodilation of resistance and capacitance vessels. *Hypertension* 2006; 48(5): 824–e105.
48. Carey RM. Angiotensin receptors and the kidney. *Curr Hypertens Rep* 1999; 1(2): 117.
49. Carey RM, Padia SH. Role of angiotensin at2 receptors in natriuresis: Intrarenal mechanisms and therapeutic potential. *Clin Exp Pharmacol Physiol*. 2013; 40(8): 527–134.
50. Kemp BA, Howell NL, Gildea JJ et al. AT<sub>2</sub> receptor activation induces natriuresis and lowers blood pressure. *Circ Res* 2014; 115(3): 388–399.
51. Culman J, Höhle S, Qadri F et al. Angiotensin as neuromodulator/neurotransmitter in central control of body fluid and electrolyte homeostasis. *Clin Exp Hypertens* 1995; 17(1–2): 281–293.
52. Steckelings UM, Kloet Ad, Summers C. Centrally mediated cardiovascular actions of the angiotensin II type 2 receptor. *Trends Endocrinol Metab* 2017; 28(9): 684–693.
53. Streeten DH, Anderson GH. Secondary hypertension. An overview of its causes and management. *Drugs* 1992; 43(6): 805–819.
54. Laragh JH, Lewis K. Dahl Memorial Lecture. The renin system and four lines for hypertension research. Nephron heterogeneity, the calcium connection, the prorenin vasodilator limb, and plasma renin and heart attack. *Hypertension* 1992; 20(3): 267–279.
55. Cohuet G, Struijker-Boudier H. Mechanisms of target organ damage caused by hypertension: Therapeutic potential. *Pharmacol Ther* 2006; 111(1): 81–98.
56. Duprez DA. Role of the renin-angiotensin-aldosterone system in vascular remodeling and inflammation: A clinical review. *J Hypertens* 2006; 24(6): 983–991.
57. Rajagopalan S, Kurz S, Münzel T et al. Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone. *J Clin Invest* 1996; 97(8): 1916–1923.
58. Nakamura K, Fushimi K, Kouchi H et al. Inhibitory effects of anti-oxidants on neonatal rat cardiac myocyte hypertrophy induced by tumor necrosis factor-alpha and angiotensin II. *Circulation* 1998; 98(8): 794–799.
59. Rodríguez-Iturbe B, Vaziri ND, Herrera-Acosta J, Johnson RJ. Oxidative stress, renal infiltration of immune cells, and salt-sensitive hypertension: All for one and one for all. *Am J Physiol Renal Physiol* 2004; 286(4): F606–F616.
60. Das UN. Is angiotensin-II an endogenous pro-inflammatory molecule? *Med Sci Monit* 2005; 11(5): RA155–RA162.
61. Paulis L, Becker STR, Lucht K et al. Direct angiotensin II type 2 receptor stimulation in N<sup>ω</sup>-nitro-L-arginine-methyl ester-induced hypertension: The effect on pulse wave velocity and aortic remodeling. *Hypertension* 2012; 59(2): 485–492.
62. Rehman A, Leibowitz A, Yamamoto N et al. Angiotensin type 2 receptor agonist compound 21 reduces vascular injury and myocardial fibrosis in stroke-prone spontaneously hypertensive rats. *Hypertension* 2012; 59(2): 291–299.
63. Sampson AK, Irvine JC, Shihata WA et al. Compound 21, a selective agonist of angiotensin AT2 receptors, prevents endothelial inflammation and leukocyte adhesion in vitro and in vivo. *Br J Pharmacol* 2016; 173(4): 729–740.
64. Yamazaki T, Komuro I, Yazaki Y. Role of the renin-angiotensin system in cardiac hypertrophy. *Am J Cardiol* 1999; 83(12A): 53H–57H.
65. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling – concepts and clinical implications: A consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol* 2000; 35(3): 569–582.
66. McKinsey TA, Olson EN. Dual roles of histone deacetylases in the control of cardiac growth. *Novartis Found Symp* 2004; 259: 132–141, discussion 141–145, 163–9.
67. Cuspidi C, Ciulla M, Zanchetti A. Hypertensive myocardial fibrosis. *Nephrol Dial Transplant* 2006; 21(1): 20–23.
68. Yamazaki T, Shiojima I, Komuro I et al. Involvement of the renin-angiotensin system in the development of left ventricular hypertrophy and dysfunction. *J Hypertens Suppl* 1994; 12(10): S153–S157.
69. Dzau VJ. Cardiac renin-angiotensin system. Molecular and functional aspects. *Am J Med* 1988; 84(3A): 22–27.
70. Faria-Costa G, Leite-Moreira A, Henriques-Coelho T. Cardiovascular effects of the angiotensin type 2 receptor. *Rev Port Cardiol* 2014; 33(7–8): 439–449.
71. Steckelings UM, Widdop RE, Paulis L, Unger T. The angiotensin AT2 receptor in left ventricular hypertrophy. *J Hypertens* 2010; 28(Suppl 1): S50–S55.
72. Oldrizzi L, Rugiu C, De Biase V, Maschio G. The place of hypertension among the risk factors for renal function in chronic renal failure. *Am J Kidney Dis* 1993; 21(5 Suppl 2): 119–123.
73. Bidani AK, Griffin KA. Pathophysiology of hypertensive renal damage: Implications for therapy. *Hypertension* 2004; 44(5): 595–601.
74. Viazzi F, Leoncini G, Ratto E et al. Microalbuminuria, blood pressure load, and systemic vascular permeability in primary hypertension. *Am J Hypertens* 2006; 19(11): 1183–1189.
75. Williams B. A potential role for angiotensin II-induced vascular endothelial growth factor expression in the pathogenesis of diabetic nephropathy? *Miner Electrolyte Metab* 1998; 24(6): 400–405.
76. Gelosa P, Pignieri A, Fändriks L et al. Stimulation of AT2 receptor exerts beneficial effects in stroke-prone rats: Focus on renal damage. *J Hypertens* 2009; 27(12): 2444–2451.
77. Kaschina E, Namsolleck P, Unger T. AT2 receptors in cardiovascular and renal diseases. *Pharmacol Res* 2017; 125(Pt A): 39–47.
78. Mergenthaler P, Dirnagl U, Meisel A. Pathophysiology of stroke: Lessons from animal models. *Metab Brain Dis* 2004; 19(3–4): 151–167.
79. Horiuchi M, Mogi M. Role of angiotensin II receptor subtype activation in cognitive function and ischaemic brain damage. *Br J Pharmacol* 2011; 163(6): 1122–1130.
80. Summers C, Horiuchi M, Widdop RE et al. Protective arms of the renin-angiotensin-system in neurological disease. *Clin Exp Pharmacol Physiol* 2013; 40(8): 580–588.
81. Krum H, Gilbert RE. Novel therapies blocking the renin-angiotensin-aldosterone system in the management of hypertension and related disorders. *J Hypertens* 2007; 25(1): 25–35.
82. Waeber B, Gavras I, Brunner HR et al. Prediction of sustained antihypertensive efficacy of chronic captopril therapy: Relationships to immediate blood pressure response and control plasma renin activity. *Am Heart J* 1982; 103(3): 384–390.
83. Kjeldsen SE, Julius S. Hypertension mega-trials with cardiovascular end points: Effect of angiotensin-converting enzyme

- inhibitors and angiotensin receptor blockers. *Am Heart J* 2004; 148(5): 747–754.
84. Maibaum J, Stutz S, Göschke R et al. Structural modification of the P2' position of 2,7-dialkyl-substituted 5(S)-amino-4(S)-hydroxy-8-phenyl-octanecarboxamides: The discovery of aliskiren, a potent nonpeptide human renin inhibitor active after once daily dosing in marmosets. *J Med Chem* 2007; 50(20): 4832–4844.
85. Parving H-H, Brenner BM, McMurray JJV et al. Cardiorenal endpoints in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012; 367(23): 2204–2213.
86. Messerli FH, Staessen JA, Zannad F. Of fads, fashion, surrogate endpoints and dual RAS blockade. *Eur Heart J* 2010; 31(18): 2205–2208.
87. Hubers SA, Brown NJ. Combined angiotensin receptor antagonism and neprilysin inhibition. *Circulation* 2016; 133(11): 1115–1124.
88. Bavishi C, Messerli FH, Kadosh B et al. Role of neprilysin inhibitor combinations in hypertension: Insights from hypertension and heart failure trials. *Eur Heart J* 2015; 36(30): 1967–1973.
89. Delyani JA. Mineralocorticoid receptor antagonists: The evolution of utility and pharmacology. *Kidney Int* 2000; 57(4): 1408–1411.
90. Young MJ. Targeting the mineralocorticoid receptor in cardiovascular disease. *Expert Opin Ther Targets* 2013; 17(3): 321–331.
91. Hallberg M, Sumners C, Steckelings UM, Hallberg A. Small-molecule AT2 receptor agonists. *Med Res Rev* 2018; 38(2): 602–624.

# STRESS, STRESS REDUCTION AND HYPERTENSION: AN UPDATED REVIEW

# 14

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## STRESS AND HYPERTENSION

### INTRODUCTION

The multifactorial pathogenesis of hypertension cannot be completely elucidated by physiological, genetic and conventional lifestyle risk factors. Growing evidence suggests the role of psychological stress in the pathogenesis of hypertension (1–3). Although over the last few decades, studies of psychosocial risk factors for hypertension have increased exponentially, questions about the underlying mechanisms, susceptibility and prevention have remained. Hence the present review explores the recent findings on psychosocial risk factors, underlying mechanisms of the stress-hypertension relationship and the evidence for stress reduction interventions for hypertension so that this knowledge may be translated into clinical prevention and management of hypertension.

If actual or perceived environmental demands surpass an individual's capacity to cope, this results in psychological stress (4). This may have acute or lasting effect on emotional, behavioural and physiological responses that predispose an individual to disease, or may affect the course of disease, such as hypertension (5–7).

In a 2017 meta-analysis of 11 studies encompassing 5696 participants, Liu et al. found psychosocial stress associated with an increased risk of hypertension (OR = 2.40, 95% CI = 1.65–3.49). The authors proposed cardiovascular reactivity as one of the underlying mechanisms of the stress-hypertension relationship (7). Gasperin et al., in the meta-analysis of six cohort studies including 23 comparison groups and 34,556 subjects, reported 21% more likelihood of developing hypertension in individuals who had greater responses to stressor tasks compared to those with lesser responses (1). Carroll et al. found high systolic blood pressure (SBP) reactivity to acute mental stress associated with increased risk of developing hypertension after a 12-year follow-up (8). It has been suggested that repeated episodes of exaggerated cardiovascular reactivity could contribute to hypertension by promoting vascular remodelling (9).

Along with increased cardiovascular reactivity, the delayed recovery to the pre-stress level is considered another possible pathway to high blood pressure (BP).

In a meta-analysis of 31 cohort studies, Chida and Steptoe found that greater stress reactivity and poor stress recovery are associated longitudinally with elevated BP, hypertension, left ventricular mass, subclinical atherosclerosis and clinical cardiac events (10).

Based on 30 years of epidemiological studies, there is a range of well-documented psychosocial stress risk factors for hypertension. These include anxiety (11), depression (12,13), anger (14), posttraumatic stress (15), low social support (16,17), occupational stress (18,19), low socioeconomic status (20), racial discrimination (21,22) and marital distress (23,24). These psychosocial risk factors are discussed in detail in [Chapter 18](#) in this volume.

### PATHWAYS LINKING PSYCHOLOGICAL STRESS TO HYPERTENSION

Physiologically, the stress response is mediated by sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenocortical (HPA) axis. These neuroendocrine systems also influence a cascade of processes involved in BP regulation (25–27). Though there is still some ambiguity in the mechanism underlying the stress-hypertension relation (28), it is believed that in individuals with genetic and psychological predispositions, repeated episodes of BP increase under stress may cause structural changes in the heart and blood vessels that result in sustained hypertension. Human and animal studies demonstrate the involvement of following pathways underlying stress-hypertension association (see [Figure 14.1](#)).

### ROLE OF SYMPATHETIC NERVOUS SYSTEM

Results from animal and human studies suggest that prolonged or repeated stress exposure causes hyperactivation of SNS and consequently increased levels of catecholamines (29,30). Increased catecholamines cause constriction of the renal, splanchnic and cutaneous vascular beds, activate the renin–angiotensin–aldosterone system (RAAS) in the kidneys (31–33) and cause endothelial dysfunction (33,34). All these will elevate BP and cause hypertension.

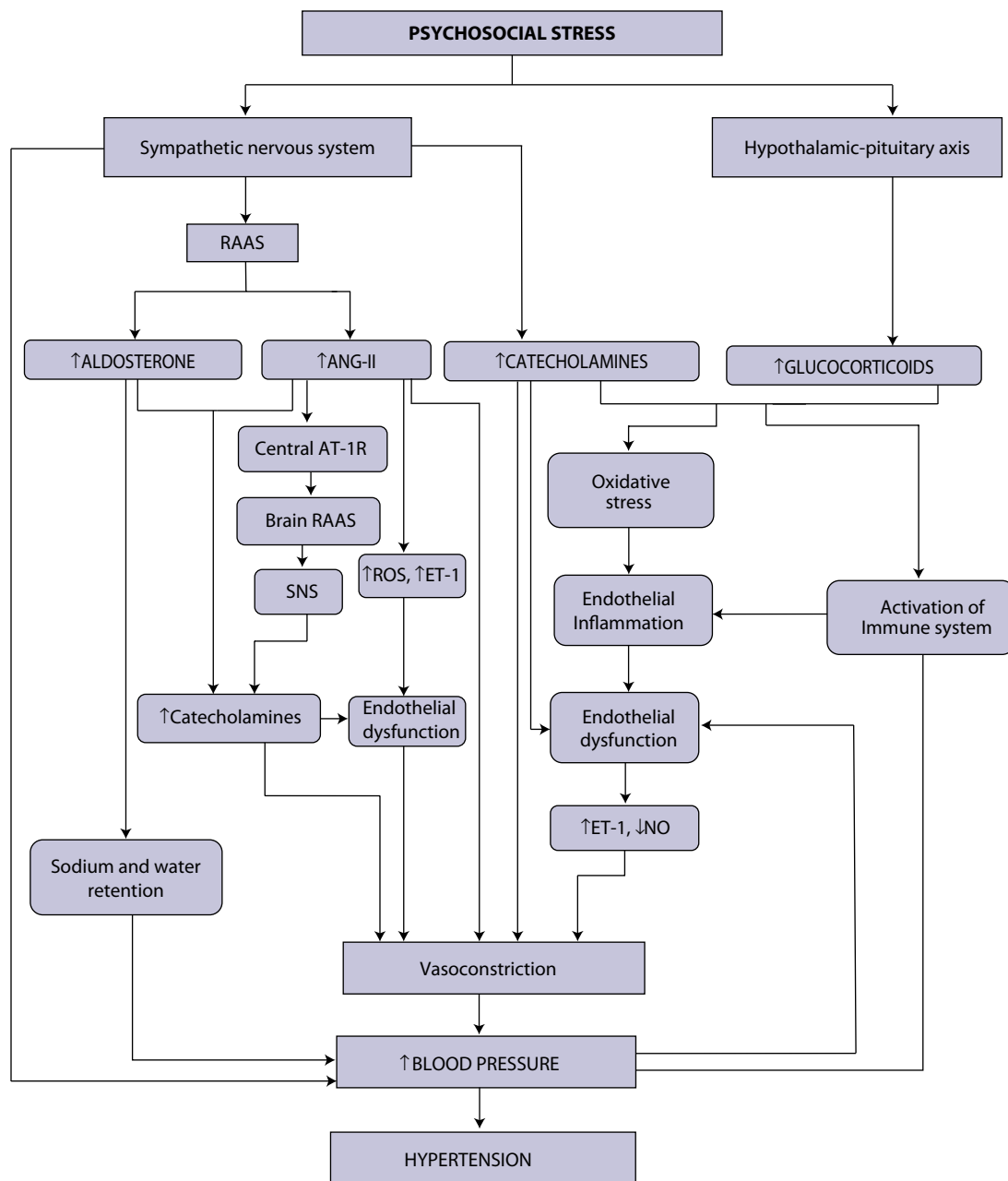


**Figure 14.1** Pathways linking psychological stress to hypertension. *Abbreviations:* RAAS, renin–angiotensin–aldosterone system; ANG-II, angiotensin -II; AT-1R, angiotensin type-1 receptors; SNS, sympathetic nervous system; ROS, reactive oxygen species; ET-1, endothelin-1; NO, nitric oxide; ↑, increase; ↓, decrease.

Stress also decreases the baroreceptor reflex response, ‘adjusting’ BP to a higher level (27,35).

### ROLE OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Stress-induced increased SNS activity and catecholamine levels activate the RAAS, which increases angiotensin-II (Ang II) and aldosterone levels. Increased aldosterone results in sodium retention, and increased Ang II causes vasoconstriction (36). Both aldosterone and Ang II

potentiate the hypertensive effect of norepinephrine (NE) by increasing its expression and inhibiting its uptake from the nerve endings (37,38). Increased Ang II levels also increase the production of endothelin-1 (ET-1) and reactive oxygen species (ROS), which leads to vasoconstriction, endothelium dysfunction and up-regulation of transcription factors such as nuclear factor- $\kappa$ B, consequently promoting vascular inflammation and causing hypertension. Increased circulating Ang II by stimulating the physiologically active angiotensin-1 receptors (AT-1R) in the brain may also contribute to the formation and release of glucocorticoids, aldosterone and catecholamine (39,40), all



of which play role in the pathogenesis of hypertension (27,32).

### ROLE OF THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS

Stress-induced activation of the HPA axis results in increase of glucocorticoid and aldosterone levels (30,41–43). Though the exact role of glucocorticoids in stress-induced hypertension is not yet fully understood, it is thought that the glucocorticoids show their BP-increasing effects by supporting the peripheral effects of catecholamines (27,44). Like catecholamines, glucocorticoids may alter the endothelial and vascular smooth muscle cell functions by triggering the secretion of ET-1, cytokines and the production of ROS in vitro (45,46). Aldosterone increases sodium and water retention, decreases NE uptake at nerve endings and has a negative effect on endothelial function (38).

### ROLE OF THE IMMUNE SYSTEM AND ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction due to repeated episodes of BP elevation under stress contributes to development of hypertension. It is suggested that repeated episodes of acute sympathetic stimulation result in sharp increases in BP which may damage the vascular endothelium and impair the release of NO, which under normal conditions causes vasodilatation and resists the effects of vasoconstrictors such as Ang II and ET-1 (47,48). In addition, ROS generated after stress reduce the production and/or bioavailability of NO (49). Acute elevations in BP are also associated with increased activation of circulating T cells that infiltrate blood vessels. These cells release proinflammatory cytokines that promote vasoconstriction and sodium retention, leading to hypertension (50–52).

### SUMMARY

Though details of pathophysiological mechanisms underlying stress-induced hypertension are not completely known, substantial evidence suggests complex interaction between the nervous, endocrine (SNS, RAAS, HPA axis) and immune systems.

## STRESS REDUCTION IN HYPERTENSION

Considering the findings that psychosocial stress contributes to development of hypertension (53,54), it is relevant to consider stress reduction interventions for treatment and prevention of hypertension.

A variety of stress reduction methods have been proposed to be useful in hypertension. A recent American Heart Association (AHA) scientific statement reviewed and recommended behavioural methods to lower BP. Based on evidence from the literature published through 2013, AHA reviewed a range of mind–body approaches to provide a class of recommendation for their implementation in clinical practice (55). In addition, Canada's 2017

Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults recommended stress management in individuals in whom stress might be contributing to high BP (56). Below, we review the existing evidence on efficacy of the most common stress reduction approaches for elevated BP, with critical updates on the data.

### TRANSCENDENTAL MEDITATION TECHNIQUE

A September 2017 scientific statement from the AHA reported that meditation practices are a widely accessible group of methods for stress reduction that may be considered as an attractive cost-effective adjunct to more traditional medical therapies for BP reduction and cardiovascular disease (CVD) prevention (57). In this scientific statement, the AHA committee did not distinguish between different types of meditation despite their heterogeneous effects on BP reduction and CVD prevention. However, the 2013 AHA scientific statement on alternative methods to lower BP did consider the evidence for different stress-reduction behavioural methods on BP (55). This included various approaches to meditation as well. The authors found that the only meditation practice that had sufficient evidence to warrant a recommendation for consideration in clinical practice was the Transcendental Meditation (TM) technique (55).

The AHA committee recommendation for TM in clinical hypertension was based on the series of systematic reviews, meta-analyses, and clinical trials that corroborated the efficacy of TM in reducing BP and cardiovascular risk (55). Among the studies considered by the scientific committee was a meta-analysis comprising nine randomized controlled trials (RCTs) of TM with 711 subjects. The investigators found significant reduction in SBP (−4.7 mmHg) and diastolic blood pressure (DBP) (−3.2 mmHg) with TM compared to control arms (58). The reduction in BP for the hypertensive subgroup was −5.1/−2.1 mmHg and for high quality studies was −6.4/−3.4 mmHg (58). A second systematic review and meta-analysis of high quality RCTs on stress reduction treatment for BP reported the average change of −5.0/−2.8 mmHg with TM (59).

Meta-analyses published after the 2013 AHA statement have confirmed the efficacy of TM in reducing BP (60,61). Bai et al. in 2015 conducted a systematic review and meta-analysis of 12 studies including 996 participants and found −4.26 mmHg reduction in SBP and −2.33 mmHg reduction in DBP with TM practice compared with control groups (60). Most recently, Ooi et al. conducted an overview of eight systematic reviews and meta-analyses that included a report by the Agency for Healthcare Research and Quality, a Cochrane systematic review, four independent reviews, and two other reviews (61). The authors found a clear trend of increasing evidence over the years supporting the efficacy of TM in lowering BP (61).

In clinical practice, TM is described as a simple, easy and natural technique for reducing stress and gaining deep rest and relaxation. It is practiced twice daily for 20 minutes while sitting in a comfortable position (62,63). Related research on the TM technique has shown significant reductions in psychological distress (64) including anxiety (65), posttraumatic stress (66) and depression (67,68).

## EFFECTS ON CARDIOVASCULAR MORBIDITY AND MORTALITY

RCTs on the TM technique have reported reduction in cardiovascular clinical events. In an RCT of 201 patients with coronary heart disease, after an average follow-up of 5.4 years there was a 48% reduction (hazard ratio 0.52; 95% CI, 0.29–0.92) in the composite of all-cause mortality, myocardial infarction or stroke in the TM practitioners compared to health education controls (69). In 202 older hypertensive patients randomly assigned to TM or controls with a mean follow-up of  $7.6 \pm 3.5$  years, TM practice was associated with a decrease in cardiovascular mortality by 30%, and 23% decrease in all-cause mortality compared with other behavioural interventions and usual care controls (70).

## MECHANISMS OF BP LOWERING

Results from a series of laboratory studies suggest that TM counteracts pathophysiologic mechanisms associated with stress. A meta-analysis of 31 studies showed significant reductions in several indicators of autonomic activity during practice of the TM compared to resting quietly with eyes closed (71). In adolescents at risk for hypertension, TM has been found to reduce cardiovascular reactivity (72) and enhance autonomic recovery to laboratory stressors (73). Studies have reported decrease in sympathetic activity (74,75), decreased plasma catecholamine levels (76), decreased adrenergic receptor sensitivity (77) and decreased cortisol (78) with TM practice.

## CONCLUSION

The concordance in BP reduction reported by several independently conducted systematic reviews, meta-analyses and scientific statements emphasize the effectiveness of the TM technique in BP reduction. The mean decreases in SBP and DBP of approximately 5 and 3 mmHg, respectively, are comparable to lifestyle modification therapies recommended by AHA and European Society of Hypertension guidelines (e.g. sodium restriction, weight loss, aerobic exercise) (79–81). In long-term RCTs, TM practice was found to decrease rates of mortality, myocardial infarction and stroke, which has not been documented for other stress-reducing approaches for hypertension to date.

## MINDFULNESS-BASED STRESS REDUCTION

Mindfulness-based stress reduction (MBSR) is another extensively practiced stress reduction program that employs an 8-week structured mindfulness meditation program to ease mental and physical suffering associated with physical, psychosomatic and psychiatric disorders (82). The individual learns the capacity to live with open and non-judgemental awareness towards all experiences within the present moment (82). In the 2013 scientific statement, the AHA committee ascribed Class III, no benefit, Level of Evidence C to MBSR (55). There was no meta-analysis available before 2013, and the available randomized and nonrandomized studies reported varied results of BP-lowering efficacy of MBSR, ranging from decrease in SBP only (83) or DBP only (84), or both (85,86), or no significant reduction in either SBP or

DBP with MBSR compared to the control group (87,88). Because of the negative or mixed results of studies, AHA did not recommend the use of MBSR in clinical practice to reduce BP (55).

Since the AHA 2013 scientific statement, more RCTs have been published that assessed the BP-lowering efficacy of MBSR. Some found MBSR effective in reducing BP (85,89), while others did not (90,91). In 2014, Abbott et al. conducted a systematic review and meta-analysis to determine the effectiveness of MBSR in patients with vascular disease (92). For assessing the efficacy of MBSR on BP reduction, they pooled the results of 4 RCTs and found moderate effect sizes of MBSR for SBP, standardized mean difference (SMD)  $-0.78$  (95% CI  $-1.46$  to  $-0.09$ ,  $p = 0.03$ ), and DBP, SMD  $-0.67$  (95% CI  $-1.26$  to  $-0.08$ ,  $p = 0.03$ ) compared to the control group (92). However, the authors did not report the change of BP in units/mmHg. In order to determine BP reduction in mmHg with MBSR, we calculated the weighted mean difference in BP by including all the RCTs published in the English language, including those in the Abbott et al. review, plus RCTs published subsequently that had assessed the effects of MBSR on BP. Seven RCTs were published through 2017 (84–86,88–91). The calculated weighted means of these trials showed  $-2.99$  mmHg in SBP and  $-1.03$  mmHg in DBP with MBSR compared to the control group (Table 14.1). Of the seven RCTs, the small study by Palta et al. (86) reported markedly different effects from the other six studies and had the smallest sample size ( $n = 20$ ). Therefore, in a sensitivity analysis, the weighted mean difference was recalculated without this study. The results showed a weighted mean difference of  $-2.36$  mmHg in SBP and  $-0.52$  mmHg in DBP with MBSR compared to the control groups (Table 14.2).

## EFFECTS ON CARDIOVASCULAR MORBIDITY AND MORTALITY

No RCTs have reported the effect of MBSR on cardiovascular clinical events as of this writing.

## MECHANISM OF BP LOWERING

The mechanisms of possible BP lowering by MBSR have not been fully elucidated, but it is proposed that MBSR reduces psychological stress and its psychological correlates. There are few studies that have assessed changes in catecholamines and cortisol, though results are heterogeneous. One study found decrease in catecholamine levels with MBSR compared to the control group (94). A few other studies reported significant decrease in cortisol levels (83,95–97) while several did not find any change in catecholamine or cortisol levels with MBSR compared to the control group (91,98–103).

## CONCLUSION

Systemic reviews and meta-analysis have suggested the efficacy of MBSR in reducing psychological stress, but the effect on physiological correlates of stress have been heterogeneous. The weighted mean BP change derived from all the randomized controlled trials published through 2017 on MBSR found modest decrease in SBP  $\sim -2$  mmHg and DBP  $\sim -1$  mmHg. No long-term effects on CVD clinical events have been documented.

**Table 14.1** Weighted mean of BP reduction with MBSR

|    | RCT                      | $\Delta$ SBP (mmHg) | $\Delta$ DBP (mmHg) | Sample size | Weight |
|----|--------------------------|---------------------|---------------------|-------------|--------|
| 1. | Hughes, 2013             | −4.1                | −3.1                | 56          | 0.089  |
| 2. | Hartman, 2012            | −6.4                | −3.5                | 110         | 0.175  |
| 3. | Blom, 2014               | 0                   | 0.4                 | 101         | 0.161  |
| 4. | Palta, 2012              | −21.92              | −16.7               | 20          | 0.031  |
| 5. | Momeni, 2016             | −13                 | −2.1                | 60          | 0.095  |
| 6. | Daubenmier, 2016         | 1                   | 1.5                 | 194         | 0.309  |
| 7. | Raja-Khan, 2017          | 0.9                 | 0.4                 | 86          | 0.137  |
|    | Mean change in BP (mmHg) | −6.217              | −3.3                |             |        |
|    | <b>Weighted mean</b>     | <b>−2.99 mmHg</b>   | <b>−1.03 mmHg</b>   | <b>627</b>  |        |

Abbreviations: RCT, randomized controlled trial;  $\Delta$ SBP, change in systolic blood pressure;  $\Delta$ DBP, change in diastolic blood pressure.

**Table 14.2** Weighted mean of BP reduction with MBSR excluding study by Palta et al.

|    | RCT                      | $\Delta$ SBP (mmHg) | $\Delta$ DBP (mmHg) | Sample Size | Weight |
|----|--------------------------|---------------------|---------------------|-------------|--------|
| 1. | Hughes, 2013             | −4.1                | −3.1                | 56          | 0.092  |
| 2. | Hartman, 2012            | −6.4                | −3.5                | 110         | 0.181  |
| 3. | Blom, 2014               | 0                   | 0.4                 | 101         | 0.166  |
| 4. | Momeni, 2016             | −13                 | −2.1                | 60          | 0.098  |
| 5. | Daubenmier, 2016         | 1                   | 1.5                 | 194         | 0.319  |
| 6. | Raja-Khan, 2017          | 0.9                 | 0.4                 | 86          | 0.141  |
|    | Mean change in BP (mmHg) | −3.6                | −1.06               |             |        |
|    | <b>Weighted mean</b>     | <b>−2.364 mmHg</b>  | <b>−0.522 mmHg</b>  | <b>607</b>  |        |

Abbreviations: RCT, randomized controlled trial;  $\Delta$ SBP, change in systolic blood pressure;  $\Delta$ DBP, change in diastolic blood pressure.

## BIOFEEDBACK

Biofeedback involves the use of automated devices to monitor physiologic indicators of states of stress/relaxation, such as muscle tension, skin temperature, skin conductance levels, heart rate or BP. When a prespecified level of the specific physiologic indicators is reached, the individual receives a feedback signal to identify and change the thoughts, emotions, behaviour and activities in an effort to lower BP. Biofeedback technique is usually used along with cognitive behavioural therapy, relaxation therapy, guided imagery and/or psychological education for greater effects on BP (104).

The results of the meta-analysis and systemic reviews of biofeedback therapy published through 2013 have been heterogeneous (59,105,106). Nakao et al. conducted meta-analysis of 22 RCTs with 905 hypertensive patients and reported simple biofeedback ineffective in reducing BP significantly as compared to control. However, they reported significantly reduced BP (SBP −7.3 mmHg, DBP −5.8 mmHg) with relaxation-assisted biofeedback compared to non-intervention but not compared to sham

or nonspecific behavioural intervention controls (106). Rainforth et al., in the meta-analysis of six trials including 141 individuals, found nonsignificant changes in SBP (−0.8 mmHg) and DBP (−2.0 mmHg) with simple biofeedback and relaxation-assisted biofeedback (+4.3/+2.4 mmHg) (59). Greenhalgh et al., in their systematic review done in 2010, did not find any evidence for the effectiveness of biofeedback in regard to hypertension control compared with placebo, no intervention, pharmacotherapy and/or behavioural therapy (105).

Although the results of meta-analyses are generally non-confirmatory, the AHA writing group in a 2013 scientific statement attributed a Class IIB, Level of Evidence B to biofeedback. AHA reasoned that heterogeneous results could be because of a variety of techniques used with biofeedback, and that these techniques may vary in their effectiveness. AHA recommendations for the consideration of use of biofeedback in clinical practice to lower BP were largely based on positive results of two trials (107,108). Of the two trials, one was by Linden et al., which included 45 subjects and reported −8/−5 mmHg decrease in BP with biofeedback compared to controls (107). The other RCT was by Nolan et al., which reported significant reduction

(−2.4/−2.1 mmHg) in BP in the relaxation-assisted biofeedback group compared to control (108).

Since the AHA 2013 scientific statement, no new meta-analysis or systemic review has been published, but a recent RCT published in 2016 on 59 prehypertensive or stage I hypertensive patients did not find significant difference in BP change between the active BP feedback group and the pseudo-feedback control group (109). Overall, we find no consistent reduction in BP with biofeedback-based reviews of meta-analyses and recent RCTs.

## EFFECTS ON CARDIOVASCULAR MORBIDITY AND MORTALITY

No study has been published that assesses the effects of biofeedback on cardiovascular clinical events.

## MECHANISMS OF BP LOWERING

The mechanisms responsible for the BP lowering induced by biofeedback when it occurs are incompletely described. There is some evidence that biofeedback alters the autonomic nervous system balance and increases baroreceptor sensitivity (105,108,110,111).

## CONCLUSION

To date, results are not consistent for effectiveness of biofeedback in hypertension.

## YOGA

The practice of yoga is historically intertwined with meditative and contemplative aspects (112). However, the forms most commonly practiced in the West are primarily physical postures or exercises, called *asanas*, and to a lesser extent, breathing exercises, called *pranayama* (112).

In its 2013 review, the AHA committee ascribed a Class III, no benefit, Level of Evidence C to yoga for BP-lowering efficacy because of the lack of available meta-analysis, methodically weak qualitative reviews (113,114) and the mixed findings of RCTs (55,115,116).

Since 2013, several meta-analysis and systemic reviews have been published on yoga's efficacy in reducing BP, and most of them reported significant BP reductions (117,118). Recent meta-analysis by Chu et al. (22 RCTs and 768 participants) found −5.21 mmHg decrease in SBP and −4.98 mmHg decrease in DBP with yoga compared to the control group (119). Similar results are reported by Park and Hans in 2017. They conducted meta-analysis of six RCTs (394 participants) and found −4.59 mmHg decrease in SBP and −3.65 mmHg reduction in DBP with yoga (120).

## EFFECTS ON CARDIOVASCULAR MORBIDITY AND MORTALITY

Available studies on yoga do not provide evidence for effects on cardiovascular clinical events, that is, morbidity or mortality (121).

## MECHANISMS OF BP LOWERING

Results from the studies suggest that yoga possibly balances the autonomic activity and thus reduces BP (93).

Whether additional pathways are involved requires future investigation.

## CONCLUSION

The evidence for the effectiveness of yoga as a treatment for hypertension shows average reductions of ~−5 mmHg SBP and ~−3 mmHg DBP. There is no current evidence for efficacy in reducing cardiovascular morbidity and mortality.

## SUMMARY

There is growing evidence that selected behavioural interventions may decrease psychosocial stress, associated high BP and its cardiovascular disease outcomes. There is substantial evidence for efficacy of TM in reducing BP and preventing cardiovascular morbidity and mortality clinical events. There is evidence that yoga practice decreases blood pressure, although long-term clinical effects are unknown. Mindfulness-based stress reduction shows small reductions in BP ~2/−1 mmHg with no data on CVD clinical events. Effects of biofeedback on BP are inconsistent to nil.

## CONCLUSIONS

In this chapter, we have summarized the current knowledge in the field on the role of stress in hypertension. A chronic stressful environment at work or related to marriage, low socioeconomic status, lack of social support, depression, anxiety, posttraumatic stress, childhood psychological trauma or racial discrimination are all demonstrated psychosocial risk factors for hypertension. Physiological mechanisms for these effects rely on activation of the sympathetic nervous system and HPA axis through repeated acute reactivity or chronic overactivity and their cascading effects.

Growing evidence suggests that high BP may be reduced by effective stress-reduction therapies. There is substantial evidence for efficacy of TM in reducing BP and preventing cardiovascular morbidity and mortality clinical events. There is evidence that yoga practice decreases BP, although long-term clinical effects are unknown. MBSR and biofeedback have small and negligible effects on BP, respectively, with no known reduction for CVD clinical outcome. The mean decrease in BP by the first two methods is comparable to other lifestyle modifications recommended by European hypertension and CVD prevention guidelines and provide a complementary method of non-pharmacological intervention for the prevention and treatment of hypertension and its cardiovascular consequences.

## REFERENCES

1. Gasperin D, Netuveli G, Dias-da-Costa JS, Pattussi MP. Effect of psychological stress on blood pressure increase: A meta-analysis of cohort studies. *Cad Saude Publica* 2009; 25(4): 715–726.
2. Spruill TM. Chronic psychosocial stress and hypertension. *Curr Hypertens Rep* 2010; 12(1): 10–16.
3. Cuffee Y, Ogedegbe C, Williams NJ et al. Psychosocial risk factors for hypertension: An update of the literature. *Curr Hypertens Rep* 2014; 16(10): 483.



4. Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. *JAMA* 2007; 298(14): 1685–1687.
5. Cohen S, Kessler RC, Gordon LU. Strategies for measuring stress in studies of psychiatric and physical disorders. In: Cohen S, Kessler R, Gordon L (eds) *Measuring Stress: A Guide for Health and Social Scientists*. Oxford University Press, New York, NY; 1995: 3–26.
6. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 1998; 338(3): 171–179.
7. Benjamin EJ, Blaha MJ, Chiuve SE et al. Heart disease and stroke statistics-2017 update: A report from the American Heart Association. *Circulation* 2017; 135(10): e146–e603.
8. Carroll D, Phillips AC, Der G et al. Blood pressure reactions to acute mental stress and future blood pressure status: Data from the 12-year follow-up of the West of Scotland Study. *Psychosom Med* 2011; 73(9): 737–742.
9. Schwartz AR, Gerin W, Davidson KW et al. Toward a causal model of cardiovascular responses to stress and the development of cardiovascular disease. *Psychosom Med* 2003; 65(1): 22–35.
10. Chida Y, Steptoe A. Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status: A meta-analysis of prospective evidence. *Hypertension* 2010; 55(4): 1026–1032.
11. Player MS, Peterson LE. Anxiety disorders, hypertension, and cardiovascular risk: A review. *Int J Psychiatry Med* 2011; 41(4): 365–377.
12. Meng L, Chen D, Yang Y et al. Depression increases the risk of hypertension incidence: A meta-analysis of prospective cohort studies. *J Hypertens* 2012; 30(5): 842–851.
13. Davidson K, Jonas BS, Dixon KE, Markovitz JH. Do depression symptoms predict early hypertension incidence in young adults in the CARDIA study? Coronary Artery Risk Development in Young Adults. *Arch Intern Med* 2000; 160(10): 1495–1500.
14. Ford CD, Sims M, Higginbotham JC et al. Psychosocial factors are associated with blood pressure progression among African Americans in the Jackson Heart Study. *Am J Hypertens* 2016; 29(8): 913–924.
15. Kibler JL, Joshi K, Ma M. Hypertension in relation to post-traumatic stress disorder and depression in the US National Comorbidity Survey. *Behav Med* 2009; 34(4): 125–132.
16. Hawkey LC, Masi CM, Berry JD, Cacioppo JT. Loneliness is a unique predictor of age-related differences in systolic blood pressure. *Psychol Aging* 2006; 21(1): 152.
17. Steptoe A, Owen N, Kunz-Ebrecht SR, Brydon L. Loneliness and neuroendocrine, cardiovascular, and inflammatory stress responses in middle-aged men and women. *Psychoneuroendocrinology* 2004; 29(5): 593–611.
18. Babu GR, Jotheeswaran AT, Mahapatra T et al. Is hypertension associated with job strain? A meta-analysis of observational studies. *Occup Environ Med* 2014; 71(3): 220–227.
19. Landsbergis PA, Dobson M, Koutsouras G, Schnall P. Job strain and ambulatory blood pressure: A meta-analysis and systematic review. *Am J Public Health* 2013; 103(3): e61–e71.
20. Matthews KA, Kiefe CI, Lewis CE et al. Socioeconomic trajectories and incident hypertension in a biracial cohort of young adults. *Hypertension* 2002; 39(3): 772–776.
21. Sims M, Diez-Roux AV, Dudley A et al. Perceived discrimination and hypertension among African Americans in the Jackson Heart Study. *Am J Public Health* 2012; 102: S258–S265.
22. Steffen PR, McNeilly M, Anderson N, Sherwood A. Effects of perceived racism and anger inhibition on ambulatory blood pressure in African Americans. *Psychosom Med* 2003; 65(5): 746–750.
23. Grewen KM, Girdler SS, Light KC. Relationship quality: Effects on ambulatory blood pressure and negative affect in a biracial sample of men and women. *Blood Press Monit* 2005; 10(3): 117–124.
24. Holt-Lunstad J, Birmingham W, Jones BQ. Is there something unique about marriage? The relative impact of marital status, relationship quality, and network social support on ambulatory blood pressure and mental health. *Ann Behav Med* 2008; 35(2): 239–244.
25. Cohen BE, Edmondson D, Kronish IM. State of the art review: Depression, stress, anxiety, and cardiovascular disease. *Am J Hypertens* 2015; 28(11): 1295–1302.
26. Davies SJ, Allgulander C. Anxiety and cardiovascular disease. *Mod Trends Pharmacopsychiatry* 2013; 29: 85–97.
27. Ayada C, Toru U, Korkut Y. The relationship of stress and blood pressure effectors. *Hippokratia* 2015; 19(2): 99–108.
28. Bobrovskaya L, Beard D, Bondarenko E et al. Does exposure to chronic stress influence blood pressure in rats? *Auton Neurosci* 2013; 177(2): 217–223.
29. Julius S, Nesbitt S. Sympathetic overactivity in hypertension. A moving target. *Am J Hypertens* 1996; 9(11): 113s–120s.
30. Golbidi S, Frisbee JC, Laher I. Chronic stress impacts the cardiovascular system: Animal models and clinical outcomes. *Am J Physiol Heart Circ Physiol* 2015; 308(12): H1476–H1498.
31. Torres SJ, Turner AI, Nowson CA. Does stress induce salt intake? *Br J Nutr* 2010; 103(11): 1562–1568.
32. Hafner S, Baumert J, Emeny RT et al. To live alone and to be depressed, an alarming combination for the renin-angiotensin-aldosterone-system (RAAS). *Psychoneuroendocrinology* 2012; 37(2): 230–237.
33. Zhang DY, Anderson AS. The sympathetic nervous system and heart failure. *Cardiol Clin* 2014; 32(1): 33–45, vii.
34. Han S, Chen X, Cox BL et al. Role of neuropeptide Y in cold stress-induced hypertension. *Peptides* 1998; 19(2): 351–358.
35. Lucini D, Di Fede G, Parati G, Pagani M. Impact of chronic psychosocial stress on autonomic cardiovascular regulation in otherwise healthy subjects. *Hypertension* 2005; 46(5): 1201–1206.
36. Givertz MM. Manipulation of the renin-angiotensin system. *Circulation* 2001; 104(5): E14–E18.
37. Triposkiadis F, Karayannis G, Giamouzis G et al. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. *J Am Coll Cardiol* 2009; 54(19): 1747–1762.
38. Adams KF. Pathophysiologic role of the renin-angiotensin-aldosterone and sympathetic nervous systems in heart failure. *Am J Health Syst Pharm* 2004; 61(Suppl 2): S4–13.
39. Yang G, Wan Y, Zhu Y. Angiotensin II—an important stress hormone. *Biol Signals* 1996; 5(1): 1–8.
40. Yang G, Xi ZX, Wan Y et al. Changes in circulating and tissue angiotensin II during acute and chronic stress. *Biol Signals* 1993; 2(3): 166–172.
41. Skowronski RJ, Feldman D. Inhibition of aldosterone synthesis in rat adrenal cells by nicotine and related constituents of tobacco smoke. *Endocrinology* 1994; 134(5): 2171–2177.
42. Hiller-Sturmhofel S, Bartke A. The endocrine system: An overview. *Alcohol Health Research World* 1998; 22(3): 153–164.
43. Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci* 2009; 10(6): 397–409.
44. Bechtold AG, Patel G, Hochhaus G, Scheuer DA. Chronic blockade of hindbrain glucocorticoid receptors reduces blood pressure responses to novel stress and attenuates adaptation to repeated stress. *Am J Physiol Regul Integr Comp Physiol* 2009; 296(5): R1445–R1454.
45. Nickel T, Deutschmann A, Hanssen H et al. Modification of endothelial biology by acute and chronic stress hormones. *Microvasc Res* 2009; 78(3): 364–369.
46. Goodwin JE, Geller DS. Glucocorticoid-induced hypertension. *Pediatr Nephrol* 2012; 27(7): 1059–1066.
47. Toda N, Nakanishi-Toda M. How mental stress affects endothelial function. *Pflugers Arch* 2011; 462(6): 779–794.
48. Williams JK, Kaplan JR, Manuck SB. Effects of psychosocial stress on endothelium-mediated dilation of atherosclerotic arteries in cynomolgus monkeys. *J Clin Invest* 1993; 92(4): 1819–1823.
49. Neves VJ, Moura MJ, Almeida BS et al. Chronic stress, but not hypercaloric diet, impairs vascular function in rats. *Stress* 2012; 15(2): 138–148.
50. Crowley SD, Song Y-S, Lin EE et al. Lymphocyte responses exacerbate angiotensin II-dependent hypertension. *Am J Physiol Regul Integr Comp Physiol* 2010; 298(4): R1089–R1097.
51. Guzik TJ, Hoch NE, Brown KA et al. Role of the T cell in the genesis of angiotensin II-induced hypertension and vascular dysfunction. *J Exp Med* 2007; 204(10): 2449–2460.
52. Miguel CD, Das S, Lund H, Mattson DL. T lymphocytes mediate hypertension and kidney damage in Dahl salt-sensitive rats. *Am J Physiol Regul Integr Comp Physiol* 2010; 298(4): R1136–R1142.
53. Farrell K, Shen BJ, Mallon S et al. Utility of the Million Behavioral Medicine Diagnostic to predict medication adherence in patients diagnosed with heart failure. *J Clin Psychol Med Settings* 2011; 18(1): 1–12.
54. Pogossova N, Saner H, Pedersen SS et al. Psychosocial aspects in cardiac rehabilitation: From theory to practice. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation of the European Society of Cardiology. *Eur J Prev Cardiol* 2015; 22(10): 1290–1306.
55. Brook RD, Appel LJ, Rubenfire M et al. Beyond medications and diet: Alternative approaches to lowering blood pressure: A scientific statement from the American Heart Association. *Hypertension* 2013; 61(6): 1360–1383.



56. Leung AA, Daskalopoulou SS, Dasgupta K et al. Hypertension Canada's 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults. *Can J Cardiol* 33(5): 557–576.
57. Levine GN, Lange RA, Bairey-Merz CN et al. Meditation and cardiovascular risk reduction: A scientific statement from the American Heart Association. *J Am Heart Assoc* 2017; 6(10).
58. Anderson JW, Liu C, Kryscio RJ. Blood pressure response to transcendental meditation: A meta-analysis. *Am J Hypertens* 2008; 21(3): 310–316.
59. Rainforth MV, Schneider RH, Nidich SI et al. Stress reduction programs in patients with elevated blood pressure: A systematic review and meta-analysis. *Curr Hypertens Rep* 2007; 9(6): 520–528.
60. Bai Z, Chang J, Chen C et al. Investigating the effect of transcendental meditation on blood pressure: A systematic review and meta-analysis. *J Hum Hypertens* 2015; 29(11): 653–662.
61. Ooi SL, Giovino M, Pak SC. Transcendental meditation for lowering blood pressure: An overview of systematic reviews and meta-analyses. *Complement Ther Med* 2017; 34: 26–34.
62. Rosenthal NE. *Transcendence: Healing and Transformation through Transcendental Meditation*. TarcherPerigee; 2012.
63. Roth B. *Strength in Stillness: The Power of Transcendental Meditation*. Simon & Schuster; 2018.
64. Nidich SI, Rainforth MV, Haaga DA et al. A randomized controlled trial on effects of the Transcendental Meditation program on blood pressure, psychological distress, and coping in young adults. *Am J Hypertens* 2009; 22(12): 1326–1331.
65. Orme-Johnson DW, Barnes VA. Effects of the transcendental meditation technique on trait anxiety: A meta-analysis of randomized controlled trials. *J Altern Complement Med* 2014; 20(5): 330–341.
66. Herron RE, Rees B. The transcendental meditation program's impact on the symptoms of post-traumatic stress disorder of veterans: An uncontrolled pilot study. *Mil Med* 2018; 183(1–2): e144–e150.
67. Elder C, Nidich S, Moriarty F, Nidich R. Effect of transcendental meditation on employee stress, depression, and burnout: A randomized controlled study. *Permanente J* 2014; 18(1): 19–23.
68. Nidich S, O'Connor T, Rutledge T et al. Reduced trauma symptoms and perceived stress in male prison inmates through the transcendental meditation program: A randomized controlled trial. *Permanente J* 2016; 20(4): 43–47.
69. Schneider RH, Grim CE, Rainforth MV et al. Stress reduction in the secondary prevention of cardiovascular disease: Randomized, controlled trial of transcendental meditation and health education in Blacks. *Circ Cardiovasc Qual Outcomes* 2012; 5(6): 750–758.
70. Schneider RH, Alexander CN, Staggers F et al. Long-term effects of stress reduction on mortality in persons > or = 55 years of age with systemic hypertension. *Am J Cardiol* 2005; 95(9): 1060–1064.
71. Dillbeck M, Orme-Johnson D. Physiological differences between transcendental meditation and rest. *Am Psychol* 1987; 42: 879–881.
72. Barnes VA, Treiber FA, Davis H. Impact of Transcendental Meditation on cardiovascular function at rest and during acute stress in adolescents with high normal blood pressure. *J Psychosom Res* 2001; 51(4): 597–605.
73. Goleman DJ, Schwartz GE. Meditation as an intervention in stress reactivity. *J Consult Clin Psychol* 1976; 44(3): 456–466.
74. Alexander CN, Swanson GC, Rainforth MV et al. Effects of the Transcendental Meditation program on stress reduction, health, and employee development: A prospective study in two occupational settings. *Anxiety Stress Coping* 1993; 6(3): 245–262.
75. Gaylord C, Orme-Johnson D, Travis F. The effects of the transcendental meditation technique and progressive muscle relaxation on EEG coherence, stress reactivity, and mental health in black adults. *Int J Neurosci* 1989; 46(1–2): 77–86.
76. Infante JR, Torres-Avisbal M, Pinel P et al. Catecholamine levels in practitioners of the transcendental meditation technique. *Physiol Behav* 2001; 72(1): 141–146.
77. Mills PJ, Schneider RH, Hill D et al. Beta-adrenergic receptor sensitivity in subjects practicing transcendental meditation. *J Psychosom Res* 1990; 34(1): 29–33.
78. Walton KG, Fields JZ, Levitsky DK et al. Lowering cortisol and CVD risk in postmenopausal women: A pilot study using the Transcendental Meditation program. *Ann N Y Acad Sci* 2004; 1032: 211–215.
79. Appel LJ, Brands MW, Daniels SR et al. Dietary approaches to prevent and treat hypertension: A scientific statement from the American Heart Association. *Hypertension* 2006; 47(2): 296–308.
80. Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31(7): 1281–1357.
81. Weber MA, Schiffrin EL, White WB et al. Clinical practice guidelines for the management of hypertension in the community: A statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens* 2014; 16(1): 14–26.
82. Kabat-Zinn J. An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: Theoretical considerations and preliminary results. *Gen Hosp Psychiatry* 1982; 4(1): 33–47.
83. Carlson LE, Speca M, Faris P, Patel KD. One year pre-post intervention follow-up of psychological, immune, endocrine and blood pressure outcomes of mindfulness-based stress reduction (MBSR) in breast and prostate cancer outpatients. *Brain Behav Immun* 2007; 21(8): 1038–1049.
84. Hartmann M, Kopf S, Kircher C et al. Sustained effects of a mindfulness-based stress-reduction intervention in type 2 diabetic patients: Design and first results of a randomized controlled trial (the Heidelberger Diabetes and Stress study). *Diabetes Care* 2012; 35(5): 945–947.
85. Hughes JW, Fresco DM, Myerscough R et al. Randomized controlled trial of mindfulness-based stress reduction for prehypertension. *Psychosom Med* 2013; 75(8): 721–728.
86. Palta P, Page G, Piferi RL et al. Evaluation of a mindfulness-based intervention program to decrease blood pressure in low-income African-American older adults. *J Urban Health* 2012; 89(2): 308–316.
87. Campbell TS, Labelle LE, Bacon SL et al. Impact of Mindfulness-Based Stress Reduction (MBSR) on attention, rumination and resting blood pressure in women with cancer: A waitlist-controlled study. *J Behav Med* 2012; 35(3): 262–271.
88. Blom K, Baker B, How M et al. Hypertension analysis of stress reduction using mindfulness meditation and yoga: Results from the HARMONY randomized controlled trial. *Am J Hypertens* 2014; 27(1): 122–129.
89. Momeni J, Omid A, Raygan F, Akbari H. The effects of mindfulness-based stress reduction on cardiac patients' blood pressure, perceived stress, and anger: A single-blind randomized controlled trial. *J Am Soc Hypertens* 2016; 10(10): 763–771.
90. Daubenmier J, Moran PJ, Kristeller J et al. Effects of a mindfulness-based weight loss intervention in adults with obesity: A randomized clinical trial. *Obesity* 2016; 24(4): 794–804.
91. Raja-Khan N, Agito K, Shah J et al. Mindfulness-based stress reduction in women with overweight or obesity: A randomized clinical trial. *Obesity* 2017; 25(8): 1349–1359.
92. Abbott RA, Whear R, Rodgers LR et al. Effectiveness of mindfulness-based stress reduction and mindfulness based cognitive therapy in vascular disease: A systematic review and meta-analysis of randomised controlled trials. *J Psychosom Res* 2014; 76(5): 341–351.
93. Innes KE, Bourguignon C, Taylor AG. Risk indices associated with the insulin resistance syndrome, cardiovascular disease, and possible protection with yoga: A systematic review. *J Am Board Fam Pract* 2005; 18(6): 491–519.
94. Kopf S, Oikonomou D, Hartmann M et al. Effects of stress reduction on cardiovascular risk factors in type 2 diabetes patients with early kidney disease—results of a randomized controlled trial (HEIDIS). *Exp Clin Endocrinol Diabetes* 2014; 122(6): 341–349.
95. Lengacher CA, Kip KE, Barta M et al. A pilot study evaluating the effect of mindfulness-based stress reduction on psychological status, physical status, salivary cortisol, and interleukin-6 among advanced-stage cancer patients and their caregivers. *J Holist Nurs* 2012; 30(3): 170–185.
96. Jensen CG, Vangkilde S, Frokjaer V, Hasselbalch SG. Mindfulness training affects attention—or is it attentional effort? *J Exp Psychol Gen* 2012; 141(1): 106–123.
97. Witek-Janusek L, Albuquerque K, Chroniak KR et al. Effect of mindfulness-based stress reduction on immune function, quality of life and coping in women newly diagnosed with early stage breast cancer. *Brain Behav Immun* 2008; 22(6): 969–981.
98. Robert McComb JJ, Tacon A, Randolph P, Caldera Y. A pilot study to examine the effects of a mindfulness-based stress-reduction and relaxation program on levels of stress hormones, physical functioning, and submaximal exercise responses. *J Altern Complement Med* 2004; 10(5): 819–827.
99. Klatt MD, Buckworth J, Malarkey WB. Effects of low-dose mindfulness-based stress reduction (MBSR-ld) on working adults. *Health Educ Behav* 2009; 36(3): 601–614.
100. Cash E, Salmon P, Weissbecker I et al. Mindfulness meditation alleviates fibromyalgia symptoms in women: Results of a randomized clinical trial. *Ann Behav Med* 2015; 49(3): 319–330.

101. Malarkey WB, Jarjoura D, Klatt M. Workplace based mindfulness practice and inflammation: A randomized trial. *Brain Behav Immun* 2013; 27(1): 145–154.
102. Rosenkranz MA, Davidson RJ, Maccoon DG et al. A comparison of mindfulness-based stress reduction and an active control in modulation of neurogenic inflammation. *Brain Behav Immun* 2013; 27(1): 174–184.
103. Nyklicek I, Mommersteeg PM, Van Beugen S et al. Mindfulness-based stress reduction and physiological activity during acute stress: A randomized controlled trial. *Health Psychol* 2013; 32(10): 1110–1113.
104. McCraty R, Atkinson M, Tomasino D. Impact of a workplace stress reduction program on blood pressure and emotional health in hypertensive employees. *J Altern Complement Med* 2003; 9(3): 355–369.
105. Greenhalgh J, Dickson R, Dundar Y. Biofeedback for hypertension: A systematic review. *J Hypertens* 2010; 28(4): 644–652.
106. Nakao M, Yano E, Nomura S, Kuboki T. Blood pressure-lowering effects of biofeedback treatment in hypertension: A meta-analysis of randomized controlled trials. *Hypertens Res* 2003; 26(1): 37–46.
107. Linden W, Lenz JW, Con AH. Individualized stress management for primary hypertension: A randomized trial. *Arch Intern Med* 2001; 161(8): 1071–1080.
108. Nolan RP, Floras JS, Harvey PJ et al. Behavioral neurocardiac training in hypertension: A randomized, controlled trial. *Hypertension* 2010; 55(4): 1033–1039.
109. Wang MY, Chang NC, Hsieh MH et al. Effect of feedback signal on blood pressure self-regulation capability in individuals with prehypertension or stage I hypertension: A randomized controlled study. *J Cardiovasc Nurs* 2016; 31(2): 166–172.
110. Lin G, Xiang Q, Fu X et al. Heart rate variability biofeedback decreases blood pressure in prehypertensive subjects by improving autonomic function and baroreflex. *J Altern Complement Med* 2012; 18(2): 143–152.
111. Chen S, Sun P, Wang S, Lin G, Wang T. Effects of heart rate variability biofeedback on cardiovascular responses and autonomic sympathovagal modulation following stressor tasks in prehypertensives. *J Hum Hypertens* 2015; 30: 105.
112. De Michelis E. *A History of Modern Yoga: Patanjali and Western Esotericism*. Continuum International Publishing Group, London, UK; 2005.
113. Yang K. A review of yoga programs for four leading risk factors of chronic diseases. *Evid Based Complement Alternat Med* 2007; 4(4): 487–491.
114. Okonta NR. Does yoga therapy reduce blood pressure in patients with hypertension?: An integrative review. *Holist Nurs Pract* 2012; 26(3): 137–141.
115. Cohen DL, Bloedon LT, Rothman RL et al. Iyengar yoga versus enhanced usual care on blood pressure in patients with prehypertension to stage I hypertension: A randomized controlled trial. *Evid Based Complement Alternat Med* 2011; 2011: 546428.
116. Cade WT, Reeds DN, Mondy KE et al. Yoga lifestyle intervention reduces blood pressure in HIV-infected adults with cardiovascular disease risk factors. *HIV Med* 2010; 11(6): 379–388.
117. Hagins M, Selfe T, Innes K. Effectiveness of yoga for hypertension: Systematic review and meta-analysis. *Evid Based Complement Alternat Med* 2013; 2013.
118. Cramer H, Lauche R, Haller H et al. Effects of yoga on cardiovascular disease risk factors: A systematic review and meta-analysis. *Int J Cardiol* 2014; 173(2): 170–183.
119. Chu P, Gotink RA, Yeh GY et al. The effectiveness of yoga in modifying risk factors for cardiovascular disease and metabolic syndrome: A systematic review and meta-analysis of randomized controlled trials. *Eur J Prevent Cardiol* 2016; 23(3): 291–307.
120. Park S-H, Han KS. Blood pressure response to meditation and yoga: A systematic review and meta-analysis. *J Altern Complement Med* 2017; 23(9): 685–695.
121. Hartley L, Dyakova M, Holmes J et al. Yoga for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2014; (5): Cd010072.



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## Section III

### Associated Risk Factors: Pathogenetic Role and Risk Modification

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# HEART RATE AS A CARDIOVASCULAR RISK FACTOR IN HYPERTENSION

# 15

Paolo Palatini

## INTRODUCTION

A large body of evidence has shown that heart rate measured in the office by healthcare personnel or with 24-hour ambulatory monitoring has a strong association with cardiovascular morbidity and mortality in general populations and in patients with diabetes, coronary artery disease and heart failure, indicating that measurement of heart rate should be an important component of cardiovascular disease risk assessment (1–5). A strong association of high heart rate with adverse outcomes has been found also in patients with hypertension in whom the risk of cardiovascular events or mortality was even doubled. The pathogenesis for the connection between elevated heart rate and cardiovascular disease may vary according to the clinical setting (1–5). In hypertension, the cardiovascular risk related to tachycardia seems to depend mainly on the clustering of several risk factors due to an underlying dysfunction of the autonomic nervous system. In this chapter, emphasis is on the relationship between high heart rate and these risk factors, and on the mechanisms for the connection between tachycardia, hypertension, obesity, metabolic syndrome and cardiovascular risk.

## HEART RATE AS PREDICTOR OF HYPERTENSION AND METABOLIC ABNORMALITIES

Previous studies have shown that about one-third of young-to-middle-aged patients with hypertension have tachycardia, high cardiac output and hyperkinetic circulation (6). Early pharmacological studies by Julius et al. have documented that this was not due to some individuals having an inherently faster cardiac pacemaker (7). After injection of  $\beta$ -blockers and atropine in two groups of normokinetic and hyperkinetic individuals, the difference in heart rate and cardiac output between the two groups was abolished. Studies based on the assay of plasma norepinephrine or heart rate variability have documented that sympathoadrenergic predominance is a common feature in hyperkinetic hypertension, and microneurographic assessment of efferent postganglionic muscle sympathetic

nerve traffic has confirmed that this condition actually reflects increased sympathetic discharge (8,9). Resting heart rate represents the balance of sympathetic and parasympathetic activity and is considered a reliable marker of autonomic nervous system tone (8,9).

In hypertensive populations, heart rate has shown a non-normal distribution with an excess of values at the upper extreme (10). Using 'mixture analysis', we could identify two distinct subgroups of subjects, a larger group with lower values of heart rate and a smaller group with higher values (10) (Figure 15.1). Blood pressure, plasma glucose, lipids and fasting insulin proved to be much higher in the subjects with high heart rate than in those with normal heart rate, especially in men. Association between fast heart rate, high blood pressure and metabolic abnormalities have been found also in other cross-sectional studies. In the PAMELA study, individuals with high blood pressure and metabolic syndrome had higher ambulatory heart rate compared to healthy controls (11). In a study in 89 obese children and adolescents, daytime and nighttime hypertension were associated with activation of the sympathoadrenal system and worse metabolic conditions (12). Similar associations were found in 6576 children aged 10–11 years from the ALSPAC (Avon Longitudinal Study of Parents and Children) study (13). The metabolic syndrome was associated with fast heart rate also in the hypertensive patients of the global cardiometabolic risk profile in patients with hypertension disease (GOOD) survey (14). Evening heart rate was associated with visceral obesity independent of body mass index and subcutaneous fat in 390 Japanese hypertensive patients (15).

An association between high heart rate, hypertension, obesity and metabolic abnormalities has been found also in longitudinal prospective studies. In the HARVEST study, both baseline and follow-up heart rates were potent predictors of subsequent development of hypertension needing drug therapy (16). In the same population, a 30% increase in risk of obesity was observed for each 10-bpm increase in baseline heart rate (17). Similarly, in a Chinese study with a 3.5-year follow-up, fast heart rate ( $>90$  bpm) was associated with a significantly higher hazard ratio of hypertension. In that study, 17 potential confounders including gender, age, body mass index, systolic and diastolic blood pressures, lipid profile and glucose levels

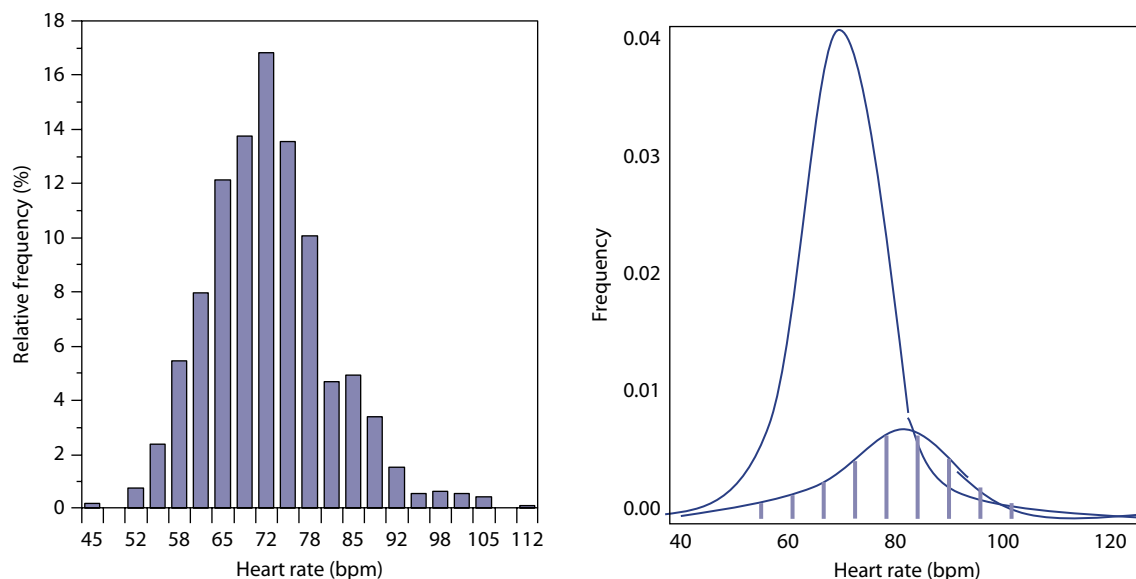


**Figure 15.1** Heart rate distribution of resting heart rate in the HARVEST study. Left panel shows a skewed distribution. The Kolmogorov-Smirnov test for normal distribution rejects normality ( $P = 0.0027$ ). Coefficient of skewness, 0.58 ( $P < 0.0001$ ). The right panel shows heart rate distribution after application of mixture analysis. Two different subpopulations have been identified, a larger one with normal heart rate and a smaller one with high heart rate. (Adapted from Palatini P et al. *Hypertension* 1997; 30: 1267–1273.)

were taken into account (18). The same group of investigators later documented that tachycardia was also a potent predictor of the metabolic syndrome (19). Similar associations were found in Japanese populations (20,21). The relationship between heart rate and the metabolic syndrome was addressed by a recent meta-analysis which included 17 cross-sectional and longitudinal prospective studies encompassing 170,000 subjects (22). This study showed that high heart rate is a potent predictor of metabolic abnormalities, with a 28% increase in risk of the metabolic syndrome for a 10-bpm increment in heart rate. The risk was more than doubled for the highest versus the lowest heart rate category.

In conclusion, the above data indicate that tachycardia primarily reflects a heightened sympathetic tone and that the sympathetic predominance is a causative factor for the development of obesity and insulin resistance in hypertension. This contention is supported by a number of longitudinal studies in which the baseline heart rate predicted future metabolic abnormalities. Particularly relevant to this issue are the results obtained in studies of heart rate variability which allows a thorough assessment of the sympatho/vagal balance (23–25).

### PROGNOSTIC VALUE OF HIGH HEART RATE IN GENERAL POPULATIONS

A relationship between tachycardia and adverse cardiovascular outcome was shown for the first time by Levy et al. (26), who found that cardiovascular mortality was higher among subjects with sustained tachycardia at baseline evaluation than among those with normal heart rate.

Several other pioneer studies confirmed that association. The correlation was particularly strong for sudden death in the Framingham Study with a sixfold increase in risk for the men in the top heart rate quintile compared to those of the bottom quintile (27). In the last 15 years, numerous new analyses that used refined statistical methods adjusting for a large number of confounders and risk factors confirmed the findings of the above-cited pioneering studies. In the Copenhagen Male Study, Jensen and colleagues (28) assessed whether a raised resting heart rate was a robust predictor of cardiovascular mortality independent of inflammation. In that study, a 10-bpm increase in heart rate was still associated with a 14% increased risk of cardiovascular mortality. A significant association between heart rate and death from cardiovascular disease was also found in a large Norwegian cohort of 180,353 men and 199,490 women aged 40–45 years (29), though the relationship was reduced when adjustments for main risk factors were made. Recent results from the MESA (Multi-Ethnic Study of Atherosclerosis) study (30) in 6766 asymptomatic participants showed that elevated resting heart rate was also associated with increased risk for incident heart failure. For 10-bpm increase in resting heart rate, there was a 40% greater adjusted relative risk of heart failure. Studies performed in Asian populations confirmed the results obtained in Western societies (31,32). In the National Survey on Circulatory Disorders, resting heart rate showed a significant association with cardiovascular and all-cause death in middle-aged men (33). Heart rate also showed a significant association with cardiac events but not with stroke. A relationship between heart rate and cardiovascular or total mortality was also found in the setting of general practises. In a prospective study of a cohort of men from 24 British towns (the British Regional

Heart Study) (34), there was a strong positive association between resting heart rate and rates of all major ischaemic heart disease events (fatal and nonfatal), ischaemic heart disease deaths and sudden cardiac death. The risk of sudden cardiac death in men with tachycardia was five times higher than in those with heart rate <60 bpm. The available evidence from general populations has been recently summarized by Zhang et al. in a meta-analysis of 46 studies, which showed that people with heart rate >80 bpm had a 45% increased risk of total mortality compared with those with heart rate <60 bpm (35). More recently, the same group of investigators found a significant association between heart rate and cardiovascular events in a meta-analysis of 45 studies (36).

### PROGNOSTIC VALUE OF HIGH HEART RATE IN HYPERTENSION

Tachycardia is a common feature in patients with hypertension. According to an Italian study performed in general practises, over 30% of hypertensive patients exhibit a heart rate >80 bpm, a cutoff frequently used to separate out tachycardia from normal heart rate (37). Using this threshold level, 27% of 1200 young grade 1 hypertensive subjects from the HARVEST study exhibited tachycardia (10). Due to the large number of people with fast heart rate, establishing whether tachycardia is a risk factor for cardiovascular disease is of great relevance in patients with hypertension.

A positive association with adverse outcome has been found in all analyses performed in hypertensive cohorts or in clinical trials of hypertensive patients. In the Framingham Study, Gillman et al. found that the relative risk of cardiovascular death adjusted for age and blood pressure was 1.68 among hypertensive men and 1.70 among hypertensive women for an increase in heart rate of 40 bpm (27). In a study by Benetos et al. in a French male population, all-cause and cardiovascular mortality steadily increased with increasing heart rates (38). In the Glasgow Blood Pressure Clinic Study (39), hypertensive patients with a heart rate persistently >80 bpm had an increased risk of all-cause and cardiovascular mortality. The highest risk of all-cause mortality was found for a final heart rate of 81–90 bpm. In the Cooper Clinic study (40), hypertensive individuals with high resting heart rate  $\geq 80$  bpm were found to be at greater risk for cardiovascular and all-cause mortality compared with those with heart rate <60 bpm. An association between heart rate and mortality was found also among the prehypertensive participants from the ARIC study (41). Subjects with heart rate  $\geq 80$  bpm had 50% higher risk of all-cause mortality than people with lower resting heart rate.

Results obtained in six clinical trials are consistent with those from the cohort studies. Elderly patients with heart rate >79 bpm from the Syst-Eur study had a 1.89 greater risk of all-cause mortality and a 1.60 greater risk of cardiovascular mortality than subjects with heart rate below that level (42). In the LIFE study, a 10-bpm increment in heart rate was associated with a 25% increased risk of cardiovascular mortality and a 27% greater risk of all-cause death (43). In the patients with hypertension and coronary artery disease from the INternational VErapamil-SR/

trandolapril Study (INVEST) study, a 5-bpm increment in resting heart rate was associated with a 6% excess risk in all-cause death, nonfatal myocardial infarction, or nonfatal stroke (44). Of particular interest are the results obtained in the VALUE study (45), in a large number of patients with high-risk hypertension. Both baseline and in-trial heart rates were powerful predictors of the composite cardiovascular outcome. The highest risk was found in the patients with tachycardia and blood pressure uncontrolled by treatment. However, the risk was elevated also in the patients with blood pressure well controlled by treatment if their heart rate was >80 bpm. This indicates that in hypertension the risk can be lowered only marginally by antihypertensive treatment if heart rate remains elevated. In the ASCOT-BPLA study (46), baseline heart rate predicted all-cause, noncardiovascular, and cardiovascular mortality that occurred during the follow-up, but not nonfatal cardiovascular events. Among the hypertensive patients from the ONTARGET and TRANSCEND studies, the risk of cardiovascular mortality increased by 77% in those with heart rate >78 bpm (47). In a prospective study of 528 patients with resistant hypertension (48) a U-shaped relationship was found between heart rate and prognosis, particularly for heart rate measured with ambulatory monitoring.

In conclusion, the data from the literature consistently demonstrate that heart rate is a potent risk factor for mortality and/or cardiovascular disease in hypertension. In all of the studies in which patients who died within the initial years of follow-up were excluded from analysis, the association between elevated heart rate and risk of cardiovascular events or mortality remained significant and did not change substantially from the risk observed in the full group thereby excluding that the relationship between heart rate and adverse outcome was due to an underlying chronic illness (5).

### PROGNOSTIC VALUE OF AMBULATORY HEART RATE

A number of experimental studies have shown that a fast heart rate has adverse effects on the circulation. The risk of pulsatile damage to vascular structure increases with higher frequency of heart beats because high heart rate exposes the arteries to increased magnitude and frequency of mechanical load, which eventually increases the stiffness of the vascular wall (49). It is thus conceivable that the overall mechanical stress exerted by heart rate on the cardiovascular system during the lifespan can be better assessed by measuring heart rate with ambulatory monitoring for 24 hours.

The relationship between ambulatory heart rate and cardiovascular events in hypertension was evaluated within the frame of the ABP-International study (50) (Figure 15.2). In age- and sex-adjusted models, both office and ambulatory heart rates were significant predictors of outcome. However, in a multivariable model that included all major cardiovascular risk factors, only ambulatory heart rate remained independently associated with cardiovascular events. Among the ambulatory heart rates, nighttime heart rate showed the strongest association with these outcomes. The superiority of ambulatory over office

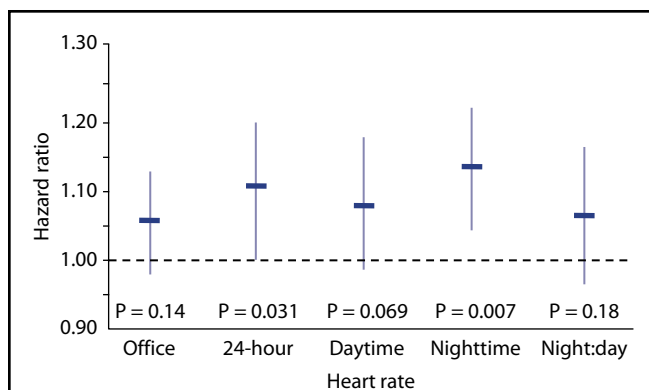


**Figure 15.2** Hazard ratios and 95% CIs for a 10-bpm increment in heart rates or a 10% increment in the night:day ratio in the ABP-International study. Results of the multivariable Cox model. Nighttime heart rate showed the closest association with risk of cardiovascular events (outcome variable). (Adapted from Palatini P et al. *Int J Cardiol* 2013; 168: 1490–1495.)

heart rate was further proved in a more recent analysis of the ABP-International data (51) (Figure 15.3). Subjects were divided into four groups according to whether they had normal or high office and nighttime heart rates. Participants with white-coat tachycardia had no increase in risk of cardiovascular events or mortality, whereas those with masked tachycardia had a risk similar to that in people with sustained tachycardia. Thus, in contrast with the results obtained from general populations (52), ambulatory heart rate added to the risk stratification for fatal combined with nonfatal cardiovascular events in the hypertensive patients from the ABP-International study. In the IDACO study and an Israeli study, ambulatory heart rate was associated with total mortality but not with cardiovascular mortality or any of the fatal combined with nonfatal cardiovascular events (53,54).

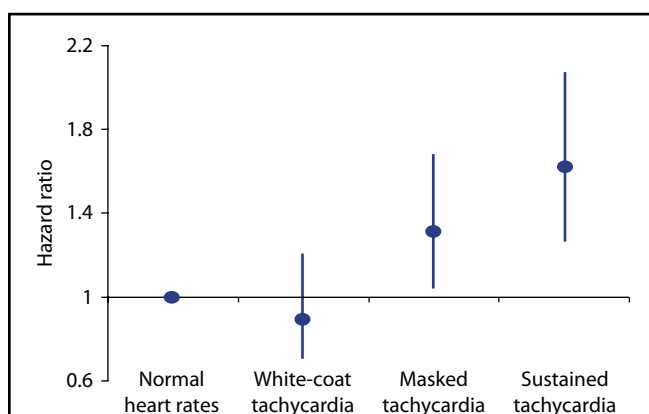


**Figure 15.3** Five-year risk of cardiovascular events (hazard ratios and 95% CIs) in 7602 participants from the ABP-International study stratified by normal or high (top quintile) office and nighttime heart rates. (Adapted from Palatini P et al. *J Hypertens* 2017; 35: 487–492.)

## HEART RATE LOWERING IN HYPERTENSION – BENEFICIAL OR DETRIMENTAL?

The pathogenetic mechanisms described above suggest that in the segment of the hypertensive population with high heart rate and autonomic dysfunction it would be rational to use a treatment that also corrects the underlying pathogenetic mechanism, restoring a normal sympatho/vagal balance. One such goal can be achieved with lifestyle measures. Sedentary habits, smoking, excessive alcohol consumption and coffee use increase the sympathetic activity, with consequent effects on resting heart rate (55). Thus trying to improve an unhealthy lifestyle should be the first goal of a clinician in the management of the hypertensive patient, especially if heart rate is elevated.

Whether pharmacological reduction of high heart rate may be beneficial in hypertension is more controversial because no results of clinical trials are available. Some authors even claimed that pharmacological heart rate lowering can have a detrimental effect in hypertension. A meta-analysis of nine clinical trials showed that the lower the heart rate achieved with treatment, the higher the total and the cardiovascular mortality (56). However, it should be pointed out that this analysis was based on aggregate data derived almost exclusively from three large clinical trials, INVEST, LIFE and ASCOT (57). If one examines the relationship between on-treatment heart rate and outcome within each of these three studies, based on individual patient data, it appears that in all studies the relationship is positive (43,44,46). Indeed, cardiovascular and total mortalities were much lower in people with low heart rate than in those with high heart rate. In a recent article, the same group of investigators attributed the claimed detrimental effect of pharmacological heart rate lowering in hypertension to a higher central blood pressure in people with low heart rate (58). In their opinion, this was due to the shift of the reflected wave from diastole to early systole at low heart rates, which would increase pulse pressure, the augmentation index and aortic stiffness.

However, several experimental data show that a low heart rate actually improves large artery distensibility. This was shown long ago by the Milan group in both rats and human beings (59). By increasing heart rate with pacing, these authors demonstrated that carotid distensibility as measured from echo Doppler progressively declined with increasing heart rate. Consistent results were obtained in human beings with measurement of pulse wave velocity. Using the same technique to increase heart rate, a French group (60) and an Australian group (61) found a progressive increase in large artery stiffness also when data were adjusted for changes in blood pressure. Recent data from the HARVEST study confirmed the negative relationship between heart rate and the augmentation index in acute studies (unpublished results). However, ambulatory heart rate showed a positive relationship with the augmentation index measured 7 years later.

## CONCLUSIONS

Given the strong association between high heart rate, overweight, insulin resistance and metabolic abnormalities,



aggressive intervention addressed to ameliorate the lifestyle could dramatically improve patients' prognosis in hypertension. Pharmacological treatments that reduce heart rate proved beneficial in patients with acute or chronic coronary syndromes and in patients with congestive heart failure (3–5). Whether this advantage can be obtained also in patients with hypertension and tachycardia is unknown. Hypertension guidelines do not recommend heart rate lowering in such patients, but this reflects their failure to recognize the overwhelming evidence about the deleterious effects of tachycardia. The absence of evidence from clinical trials should not be considered as evidence that heart rate should not be decreased. Antihypertensive drugs have different effects on the components of the cardiometabolic risk, and thus in this condition antihypertensive treatment could be tailored according to the presence of risk factors. Theoretically, drugs which decrease blood pressure and heart rate through a reduction of the sympathetic outflow should be more beneficial in clinical situations characterized by heightened sympathetic activity associated with insulin resistance. However, these drugs often have important side effects and are no longer considered as first-line therapy in hypertension. Beta-blockers have favourable effects on heart rate but may have untoward effects on metabolic variables (62). Thus traditional beta-blockers are not indicated for hypertensive patients with metabolic abnormalities. At variance, beta-blockers such as carvedilol or nebivolol, which have a more favourable effect on the lipid profile and insulin resistance compared with older beta-blockers (62,63), are not contraindicated. Blockade of the angiotensin II type 1 receptor may have the additional benefit of producing a sympathoinhibitory activity accompanied by an improvement in insulin sensitivity (64). Whether these conceptual advantages can be translated into effective benefits should be confirmed by future studies.

## REFERENCES

- Palatini P. Elevated heart rate in cardiovascular diseases: A target for treatment? *Prog Cardiovasc Dis* 2009; 52: 46–60.
- Reil JC, Bohm M. The role of heart rate in the development of cardiovascular disease. *Clin Res Cardiol* 2007; 96: 585–592.
- Palatini P, Benetos A, Grassi G et al. European Society of Hypertension: Identification and management of the hypertensive patient with elevated heart rate: Statement of a European Society of Hypertension Consensus Meeting. *J Hypertens* 2006; 24: 603–610.
- Fox KM, Ferrari R. Heart rate: A forgotten link in coronary artery disease? *Nat Rev Cardiol* 2011; 8: 369–379.
- Palatini P. Role of elevated heart rate in the development of cardiovascular disease in hypertension. *Hypertension* 2011; 58: 745–750.
- Julius S, Krause L, Schork NJ et al. Hyperkinetic borderline hypertension in Tecumseh, Michigan. *J Hypertension* 1991; 9: 77–84.
- Julius S, Pascual, London R. Role of parasympathetic inhibition in the hyperkinetic type of borderline hypertension. *Circulation* 1971; 44: 413–418.
- Grassi G, Arenare F, Quarti-Trevano F et al. Heart rate, sympathetic cardiovascular influences, and the metabolic syndrome. *Prog Cardiovasc Dis* 2009; 52: 31–37.
- Mancia G, Bousquet P, Elghozi JL et al. The sympathetic nervous system and the metabolic syndrome. *J Hypertens* 2007; 25: 909–920.
- Palatini P, Casiglia E, Pauletto P, et al. Relationship of tachycardia with high blood pressure and metabolic abnormalities. A study with mixture analysis in three populations. *Hypertension* 1997; 30: 1267–1273.
- Mancia G, Bombelli M, Corrao G et al. Metabolic syndrome in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study: Daily life blood pressure, cardiac damage, and prognosis. *Hypertension* 2007; 49: 40–47.
- Gilardini L, Parati G, Sartorio A et al. Sympathoadrenergic and metabolic factors are involved in ambulatory blood pressure rise in childhood obesity. *J Hum Hypertens* 2008; 22: 75–82.
- Charakida M, Jones A, Falaschetti E et al. Childhood obesity and vascular phenotypes: A population study. *J Am Coll Cardiol* 2012; 60: 2643–2650.
- Perlini S, Naditch-Brule L, Farsang C et al. Pulse pressure and heart rate in patients with metabolic syndrome across Europe: Insights from the GOOD survey. *J Hum Hypertens* 2013; 27: 412–416.
- Yano Y, Haimoto H, Hoshida S et al. Evening heart rate measured at home is associated with visceral obesity and abnormal fat distribution in patients with hypertension. *Am J Hypertens* 2011; 24: 783–788.
- Palatini P, Dorigatti F, Zaetta V et al. Heart rate as a predictor of development of sustained hypertension in subjects screened for stage 1 hypertension: The HARVEST Study. *J Hypertens* 2006; 24: 1873–1880.
- Palatini P, Mos L, Santonastaso M et al. Resting heart rate as a predictor of body weight gain in the early stage of hypertension. *Obesity* 2011; 19: 618–623.
- Wang A, Liu X, Guo X et al. Resting heart rate and risk of hypertension: Results of the Kailuan cohort study. *J Hypertens* 2014; 32: 1600–1605.
- Jiang X, Liu X, Wu S et al. Metabolic syndrome is associated with and predicted by resting heart rate: A cross-sectional and longitudinal study. *Heart* 2015; 101: 44–49.
- Masuo K, Kawaguchi H, Mikami H et al. Serum uric acid and plasma norepinephrine concentrations predict subsequent weight gain and blood pressure elevation. *Hypertension* 2003; 42: 474–480.
- Shigetoh Y, Adachi H, Yamagishi S et al. Higher heart rate may predispose to obesity and diabetes mellitus: 20-year prospective study in a general population. *Am J Hypertens* 2009; 22: 151–155.
- Liu X, Luo X, Liu Y et al. Resting heart rate and risk of metabolic syndrome in adults: A dose-response meta-analysis of observational studies. *Acta Diabetol* 2017; 54: 223–235.
- Palatini P, Longo D, Zaetta V et al. Evolution of blood pressure and cholesterol in stage 1 hypertension: Role of autonomic nervous system activity. *J Hypertens* 2006; 24: 1375–1381.
- Palatini P, Majahalme S, Amerena J et al. Determinants of left ventricular mass in young subjects with sympathetic overactivity. The Tecumseh Offspring Study. *J Hypertens* 2000; 18: 769–775.
- Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *Int J Cardiol* 2010; 141: 122–131.
- Levy RL, White PD, Stroud WD et al. Transient tachycardia: Prognostic significance alone and in association with transient hypertension. *JAMA* 1945; 129: 585, 88.
- Gillman MW, Kannel WB, Belanger A, D'Agostino RB. Influence of heart rate on mortality among persons with hypertension: The Framingham Study. *Am Heart J* 1993; 125: 1148–1154.
- Jensen MT, Marott JL, Allin KH et al. Resting heart rate is associated with cardiovascular and all-cause mortality after adjusting for inflammatory markers: The Copenhagen City Heart Study. *Eur J Prev Cardiol* 2012; 19: 102–108.
- Tverdal A, Hjellvik V, Selmer R. Heart rate and mortality from cardiovascular causes: A 12 year follow-up study of 379,843 men and women aged 40–45 years. *Eur Heart J* 2008; 29: 2772–2781.
- Opdahl A, Ambale Venkatesh B et al. Resting heart rate as predictor for left ventricular dysfunction and heart failure: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2014; 63: 1182–1189.
- Okamura T, Hayakawa T, Kadowaki T et al. Resting heart rate and cause-specific death in a 16.5-year cohort study of the Japanese general population. *Am Heart J* 2004; 147: 1024–1032.
- Fujiura Y, Adachi H, Tsuruta M et al. Heart rate and mortality in a Japanese general population: An 18-year follow-up study. *J Clin Epidemiol* 2001; 54: 495–500.
- Makita S, Onoda T, Ohsawa M et al. Bradycardia is associated with future cardiovascular diseases and death in men from the general population. *Atherosclerosis* 2014; 236: 116–120.
- Shaper AG, Wannamethee G, Macfarlane PW et al. Heart rate, ischaemic heart disease, and sudden cardiac death in middle-aged British men. *Br Heart J* 1993; 70: 49–55.
- Zhang D, Shen X, Qi X. Resting heart rate and all-cause and cardiovascular mortality in the general population: A meta-analysis. *CMAJ* 2016; 188: E53–E63.
- Zhang D, Wang W, Li F. Association between resting heart rate and coronary artery disease, stroke, sudden death and non-cardiovascular diseases: A meta-analysis. *CMAJ* 2016; 188(18): E384–E392.



37. Farinaro E, Stranges S, Guglielmucci G et al. Heart rate as a risk factor in hypertensive individuals. The Italian TensioPulse Study. *Nutr Metab Cardiovasc Dis* 1999; 9: 196–202.
38. Benetos A, Rudnichi A, Thomas F et al. Influence of heart rate on mortality in a French population: Role of age, gender and blood pressure. *Hypertension* 1999; 33: 44–52.
39. Paul L, Hastie CE, Li WS et al. Resting heart rate pattern during follow-up and mortality in hypertensive patients. *Hypertension* 2010; 55: 567–574.
40. Saxena A, Minton D, Lee DC et al. Protective role of resting heart rate on all-cause and cardiovascular disease mortality. *Mayo Clin Proc* 2013; 88: 1420–1426.
41. King DE, Everett CJ 3rd, Mainous AG, Liszka HA. Long-term prognostic value of resting heart rate in subjects with prehypertension. *Am J Hypertens* 2006; 19: 796–800.
42. Palatini P, Thijs L, Staessen JA et al. Predictive value of clinic and ambulatory heart rate for mortality in elderly subjects with systolic hypertension. *Arch Intern Med* 2002; 162: 2313–2321.
43. Okin PM, Kjeldsen SE, Julius S et al. All-cause and cardiovascular mortality in relation to changing heart rate during treatment of hypertensive patients with electrocardiographic left ventricular hypertrophy. *Eur Heart J* 2010; 31: 2271–2279.
44. Kolloch R, Legler UF, Champion A et al. Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: Findings from the INternal VERapamil-SR/trandolapril STudy (INVEST). *Eur Heart J* 2008; 29: 1327–1334.
45. Julius S, Palatini P, Kjeldsen SE et al. Usefulness of heart rate to predict cardiac events in treated patients with high-risk systemic hypertension. *Am J Cardiol* 2012; 109: 685–692.
46. Poulter NR, Dobson JE, Sever PS et al. Baseline heart rate, antihypertensive treatment, and prevention of cardiovascular outcomes in ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial). *J Am Coll Cardiol* 2009; 54: 1154–1161.
47. Lonn EM, Rambihar S, Gao P et al. Heart rate is associated with increased risk of major cardiovascular events, cardiovascular and all-cause death in patients with stable chronic cardiovascular disease: An analysis of ONTARGET/TRANSCEND. *Clin Res Cardiol* 2014; 103: 149–159.
48. Salles GF, Cardoso CR, Fonseca LL et al. Prognostic significance of baseline heart rate and its interaction with beta-blocker use in resistant hypertension: A cohort study. *Am J Hypertens* 2013; 26: 218–226.
49. Giannoglou GD, Chatzizisis YS, Zamboulis C et al. Elevated heart rate and atherosclerosis: An overview of the pathogenetic mechanisms. *Int J Cardiol* 2008; 126: 302–312.
50. Palatini P, Reboldi G, Beilin LJ et al. Predictive value of night-time heart rate for cardiovascular events in hypertension. The ABP-International study. *Int J Cardiol* 2013; 168: 1490–1495.
51. Palatini P, Reboldi G, Beilin LJ et al. Masked tachycardia. A predictor of adverse outcome in hypertension. *J Hypertens* 2017; 35: 487–492.
52. Hozawa A, Inoue R, Ohkubo T et al. Predictive value of ambulatory heart rate in the Japanese general population: The Ohasama Study. *J Hypertens* 2008; 26: 1571–1576.
53. Hansen TW, Thijs L, Boggia J et al. Prognostic value of ambulatory heart rate revisited in 6928 subjects from 6 populations. *Hypertension* 2008; 52: 229–235.
54. Ben-Dov IZ, Kark JD, Ben-Ishay D et al. Blunted heart rate dip during sleep and all-cause mortality. *Arch Intern Med* 2007; 167: 2116–2121.
55. Grassi G. Counteracting the sympathetic nervous system in essential hypertension. *Curr Opin Nephrol Hypertens* 2004; 13: 513–519.
56. Bangalore S, Sawhney S, Messerli FH. Relation of beta-blocker-induced heart rate lowering and cardioprotection in hypertension. *J Am Coll Cardiol* 2008; 52: 1482–1489.
57. Palatini P. Heart rate reduction and cardiovascular outcome in hypertension. *J Am Coll Cardiol* 2017; 69: 1099–1100.
58. Messerli FH, Rimoldi SF, Bangalore S et al. When an increase in central systolic pressure overrides the benefits of heart rate lowering. *J Am Coll Cardiol* 2016; 68: 754–762.
59. Mangoni AA, Mircoli L, Giannattasio C et al. Heart rate-dependence of arterial distensibility *in vivo*. *J Hypertens* 1996; 14: 897–901.
60. Lantelme P, Mestre C, Lievre M et al. Heart rate: An important confounder of pulse wave velocity assessment. *Hypertension* 2002; 39: 1083–1087.
61. Tan I, Spronck B, Kiat H et al. Heart rate dependency of large artery stiffness. *Hypertension* 2016; 68: 236–242.
62. Grassi G, Trevano FQ, Facchini A et al. Efficacy and tolerability profile of nebivolol vs atenolol in mild-to-moderate essential hypertension: Results of a double-blind randomized multicentre trial. *Blood Press* 2003; 2: 35–40.
63. Bakris GL, Fonseca V, Katholi RE et al. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: A randomized controlled trial. *JAMA* 2004; 292: 2227–2236.
64. Dominguez LJ, Barbagallo M, Jacober SJ et al. Bisoprolol and captopril effects on insulin receptor tyrosine kinase activity in essential hypertension. *Am J Hypertens* 1997; 10: 1349–1355.

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## EPIDEMIOLOGY OF OBESITY

Despite the well-established contribution of overweight and obesity to the development of hypertension, metabolic abnormalities (i.e. diabetes type 2, dyslipidemia etc.), sleep-disordered breathing, cardiovascular (CV) disease, stroke, kidney disease, arrhythmia and heart failure (Figure 16.1), the global prevalence of obesity has nearly tripled over the past four decades. According to the World Health Organization, in 2016 more than 1.9 billion (39%) adults were overweight, of whom over 650 million (13%) were obese. The higher rate of overweight was found in women (40%) when compared to men (39%) with similar greater rates for obesity in women (15%) than men (11%). The rapidly rising levels of excess body weight and obesity have also raised concerns in children and adolescents aged 5–19 years, reaching a total number of over 340 million in 2016, demonstrating an increase from just 4% to over 18% between the years 1975 and 2016. The alarming rise in incidence of excess body weight and obesity in children and adolescents indicates that obesity-related health conditions, previously evident mainly in adulthood, are likely to increase in younger populations, leaving them at increased risk for future adverse CV and metabolic consequences, and health-related quality of life. Obese children are at higher risk of developing sleep-disordered breathing including snoring, obstructive sleep apnoea (OSA) and even central apnoea followed by oxygen desaturation and/or bradycardia. While this chapter focuses on adult obesity-related OSA, the prevalence of OSA is high and ranges from 46 to 59% in obese children and adolescents (1). Undoubtedly, low-cost effective weight loss interventions are clearly warranted in reducing the global burden attributable to obesity.

## DEFINITION AND DIAGNOSIS OF OBSTRUCTIVE SLEEP APNOEA

### DEFINITION

Sleep-disordered breathing is an umbrella term that refers to the clinical syndrome caused by partial or complete

cessation of breathing that occurs mainly throughout the night (2). Amongst sleep-disordered breathing, OSA is the most common type of sleep apnoea, characterized by recurrent episodes of narrowing and/or closure of the upper respiratory airflow resulting in shallow or paused breathing, intermittent oxyhaemoglobin desaturation and arousal associated with maintained or increasing ventilator efforts (3).

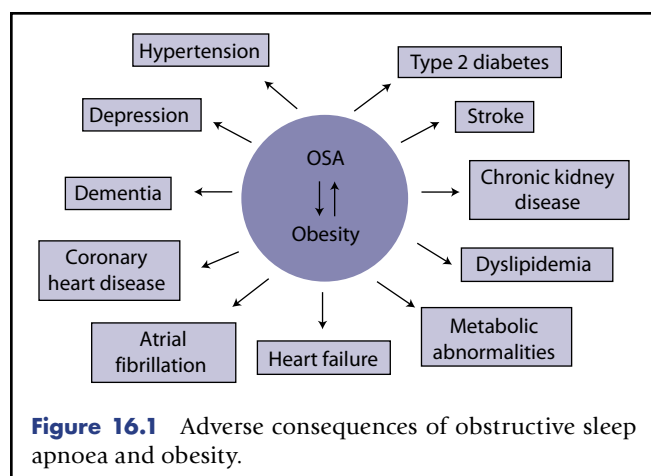
### SYMPTOMS

The most common signs and symptoms indicative of OSA include excessive daytime sleepiness, often insomnia, loud snoring, abrupt awakenings accompanied by gasping or choking, episodes of breathing cessation observed by a partner, nocturia, morning headache, elevated blood pressure (BP) (i.e. non-dipping profile in ambulatory readings, resistant hypertension), difficulty concentrating, mood changes (depression, irritability), decreased libido and erectile dysfunction. Subjects with OSA are at increased risk of motor vehicle accidents. Therefore, early detection and identification of patients with sleep apnoea is integral in daily clinical practise.

### DIAGNOSIS

Numerous tools for screening OSA are available and have been validated in various populations and clinical scenarios. The Berlin Questionnaire (BQ) has a high internal validity and is useful to identify patients with sleep apnoea in the general population. However, the diagnostic accuracy of the BQ in detecting OSA in patients post myocardial infarction (4) and in patients with resistant hypertension (5) was low, and not useful in the prediction of sleep-disordered breathing in a study of a population referred to a sleep clinic centre (6,7).

The Epworth Sleepiness Scale (ESS) is another self-reported test to assess the propensity for daytime sleepiness or dozing in different situations. However, scores obtained from the ESS have been found comparable in individuals with or without sleep-disordered breathing



(7). Overall, the quality of available evidence derived from numerous studies comparing the use of ESS against polysomnography (PSG) across apnoea-hypopnea index (AHI) cutoffs is low (8).

Other recognised screening tools of note include the STOP questionnaire (snoring, tiredness, observed apnoea, high BP) and the STOP-Bang Questionnaire which in addition to the STOP test evaluates body mass index (BMI), age, neck circumference and gender. The STOP questionnaire demonstrates moderate to high sensitivity, low specificity and moderate accuracy. The STOP-Bang questionnaire has a high sensitivity and low specificity for detecting OSA; however, this substantially improves with the higher levels of AHI cutoffs (8). Indeed, a high STOP-Bang score has demonstrated high sensitivity and probability in detecting moderate-to-severe OSA and was found to be comparable to home or laboratory PSG (9). In addition, the sensitivity of the STOP-Bang questionnaire in predicting OSA can be further improved following the measurement of serum bicarbonate (10). A recent meta-analysis of 17 studies with a total of 9206 patients confirmed the high performance of the STOP-Bang questionnaire for screening OSA in the sleep clinic and surgical population (11). A higher STOP-Bang score has been linked to the greater probability of moderate-to-severe OSA (11).

While these questionnaires are helpful in screening OSA, available evidence indicates the potential risk for bias including false-positive and false-negative results. Therefore, self-reported tests cannot be used for OSA diagnosis in the absence of PSG – the gold standard technique, or home sleep apnoea testing with a technically adequate device in uncomplicated patients with a high OSA pre-test probability (8).

Patients presenting with typical OSA symptoms (e.g. hypersomnolence, sleep-time choking, snoring, observed apnoeas) are diagnosed if five or more scoreable respiratory events (predominantly obstructive or mixed apnoeas, hypopnoeas or respiratory effort-related arousals [RERAs]) per hour of sleep are reported on PSG. Alternatively, 15 respiratory events per hour of sleep on reporting PSG justifies diagnosis, irrespective of patient's complaints (12). Based on the index denoting average number of apnoeic and hypopnoeic episodes per hour of sleep (AHI) or obstructive respiratory disturbance index (RDI) if RERAs are considered, OSA is classified as follows: mild, AHI  $\geq 5$  and  $<15$  events per hour; moderate,

AHI  $\geq 15$  and  $\leq 30$  events per hour; and severe, AHI  $>30$  events per hour (13).

Notably, current clinical and research studies used inconsistent definition of a hypopnea event (flow reduction  $\geq 30\%$  for  $>10$  seconds associated with a  $\geq 3\%$  oxygen desaturation or a cortical arousal, or a  $\geq 4\%$  oxygen desaturation without consideration of cortical arousals). This has therefore impacted on the AHI levels in a given individual and disease severity, resulting in diverse prevalence values for sleep-disordered breathing (8,13,14).

## PREVALENCE OF OSA

Despite growing evidence linking OSA to increased CV risk, improvements in diagnosis and treatment, OSA still remains highly prevalent, often underdiagnosed and undertreated, in both the general population and in a large proportion of patients receiving regular CV treatment. A recent study which included a sample of the general population ( $n = 415$ ) aged 40–65 years found that 24.1% had mild OSA, 15.4% moderate-to-severe disease and 3.6% had already received OSA-treatment (15). Moreover, although one in five individuals demonstrated moderate-to-severe OSA, the majority of these subjects were asymptomatic or had minimal symptoms (15).

Further, evidence for the need to improve awareness of sleep-disordered breathing comes from a prospective study of a total of 500 consecutive outpatients equally included from five clinical subspecialties in which patients were treated for hypertension, coronary disease, arrhythmia, heart failure and valvular heart disease (16). The risk of OSA was primarily assessed by the use of the BQ, previous diagnosis and treatment for OSA. This study found that 51.6% ( $n = 258$ ) of patients had a high risk for OSA, of whom only 3.1% ( $n = 13$ ) had been previously diagnosed and only six patients were treated for OSA. A high prevalence of OSA (66%), varying from 50 (hypertension group) to 80% (HF group) indicates that OSA is also underdiagnosed in several cardiology subspecialties (16), highlighting an unmet need to raise awareness of sleep-disordered breathing.

It is noteworthy that the prevalence of OSA varies considerably and depends on testing methodology and scoring criteria used for the respiratory events. Utilizing an AHI cutoff of  $\geq 5$  events per hour (hypopnea event defined as a  $\geq 4\%$  reduction in oxyhaemoglobin saturation), the prevalence of OSA has been estimated at 14% in men and 5% in women (17). Within the same selected urban population, 13% of men and 6% of women demonstrated moderate-to-severe OSA (AHI  $\geq 15$  events per hour) (17). However, the estimated prevalence of sleep-disordered breathing can range from approximately 14% up to 55% depending on age group, gender and severity of the disease (17).

A large discrepancy in OSA prevalence has been confirmed in a recent systematic review of 24 cross-sectional studies and the cross-sectional components of longitudinal studies conducted in all world regions (18). The heterogeneity amongst the included studies (i.e. sampling methods, diagnostic criteria, methods used to measure airflow, etc.) had an impact on the reported prevalence of OSA which considerably varies depending on the diagnostic criteria used, age, gender and study population (18). Nevertheless, the overall prevalence of OSA using the AHI of  $\geq 5$  events per hour, in the general adult population

ranged from 9 to 38% and increased with the degree of obesity. Obese men and women had a higher incidence of OSA compared to their overweight counterparts. It also increased with ageing, with the highest peak at 90% for men and 78% for women aged 60–85 years (18). However, despite an observed increase with age, OSA at AHI of  $\geq 15$  events per hour was less prevalent in the elderly, accounting for 6–17%, reaching 49% in the advanced age group. While these findings confirm that a higher BMI, advanced age and male gender increases the risk of OSA, the exact prevalence of OSA still needs to be determined by a uniform methodology (e.g. type 1 PSG vs. polygraphic recordings), and diagnostic threshold in future studies.

### INTERACTION BETWEEN OSA AND OBESITY

Obesity is the most important contributor to the development and progression of OSA. The relationship between weight change and the change in OSA severity comes from the longitudinal prospective Wisconsin Sleep Cohort Study in which 690 randomly selected representatives underwent PSG twice within a 4-year interval (19). In this study, a 10% weight gain predicted an approximate 32% increase in the AHI and a sixfold increase in the likelihood of developing moderate-to-severe sleep-disordered breathing. On the contrary, a 10% weight loss was associated with a 26% decrease in the AHI (19), indicating that weight management is an effective approach for the prevention and remission of OSA. These findings have been supported by the results from the Sleep Heart Health Study in which a total of 2968 men and women were followed over with a 5-year duration (20). With a given increase in weight gain, men were more likely to have an increase in RDI compared to women, and this was independent of differences in initial weight, waist circumference, age or ethnicity (20).

A strong and independent association of overweight and obesity with the development of severe-to-moderate OSA confirmed by PSG has been indicated in a cohort of 1042 volunteers (21). The risk of OSA was 10.5-fold higher among obese subjects compared to individuals with normal BMI.

In fact, the prevalence of moderate-to-severe OSA in obese patients with BMI  $\geq 30$  kg/m<sup>2</sup> has been found to exceed 50% (22), reaching as high as 71.4% in the severely obese group (BMI 35.0–39.9 kg/m<sup>2</sup>), 74% in the morbidly obese group (BMI 40.0–40.9 kg/m<sup>2</sup>), and even higher percentage of OSA with greater degrees of obesity in patients undergoing bariatric surgery for weight loss (23). Notably, severe OSA with an average of total RDI  $88.9 \pm 42$  (standard deviation [SD]) has been noted in more than 75% of morbidly obese patients undergoing bariatric surgery (24). Amongst numerous variables, snoring, the STOP-Bang score  $\geq 3$ , fatty liver and BMI were significantly associated with OSA when compared to subjects without OSA (24). BMI and dyslipidemia were directly linked to the severity of OSA in this morbidly obese cohort (24).

Importantly, among obese patients, abdominal (visceral) fat rather than subcutaneous or generalized (total) body fat seems to be a critical contributor to the development of OSA (25,26). In fact, despite comparable BMI levels or subcutaneous or total body fat distribution, a significantly higher amount of visceral fat has been found in OSA patients when compared to obese control subjects (25). Central obesity accompanied by increased abdominal

fat promotes metabolic abnormalities including insulin resistance and dyslipidemia leading to hypertension, type 2 diabetes and adverse CV sequelae (27). The predictive value of regional (abdominal) body fat distribution (but not fat accumulation in the neck or pharyngeal region) for the presence and severity of OSA has been confirmed by the findings from yet another study (26).

### OBESITY ATTRIBUTABLE TO OSA

It is not only obesity that triggers the development of OSA, but surprisingly there is growing evidence that the converse is also possible. Sleep-disordered breathing with resultant sleep deprivation, daytime sleepiness, tiredness and lack of physical activity are important adverse contributors to accelerated body weight. Patients with sleep apnoea have the propensity for a rapid increase in weight gain a year preceding the onset of disease (28). In contrast, no significant weight changes have been observed in obese subjects without sleep apnoea (28). Amongst numerous contributing factors, a lack of regular exercise and depression have also been demonstrated as significant independent predictors of excessive daytime sleepiness independent of age, BMI, gender, diabetes and central nervous system medication use in patients with sleep apnoea (29).

Previous experimental, epidemiological and prospective studies have demonstrated that sleep deprivation and poor quality of nighttime sleep adversely affects metabolic and neuroendocrine regulation, resulting in increased calorie intake, thereby playing a critical role in the development of obesity (30–32). In fact, a sleep duration of less than 5 hours has been linked to central body fat distribution and increased percentage of body fat compared to sleep time of an average of 7–8 hours, and these associations persisted following the adjustment for sleep apnoea, insomnia or daytime sleepiness (30). Moreover, despite unchanged plasma glucose levels, even an acute total sleep loss has been found to enhance centrally mediated responses to hedonistic food stimuli and hunger compared to normal sleep (32).

The association between OSA and clinical outcomes including the incident of hypertension, type 2 diabetes, metabolic abnormalities, coronary heart disease, heart failure, ischaemic stroke, chronic kidney disease, depression, dementia and higher risk of mortality is well established (Figure 16.1) and has been discussed elsewhere (33,34).

### MECHANISMS UNDERLYING OSA

#### ROLE OF THE SYMPATHETIC NERVOUS SYSTEM

OSA and obesity share multiple pathophysiological mechanisms resulting in adverse consequences on various organs, with sympathetic nervous system activation playing a pivotal role in this scenario (33). Microneurography studies have documented high levels of muscle sympathetic nerve activity (MSNA) in OSA patients during wakefulness, with further increase during sleep (35). Repetitive episodes of apnoea and hypopnea events and the resultant intermittent hypoxemia during sleep alter sympathetic CV regulation, leading to augmented sympathetic drive. Recurrent incidents of hypoxemia in OSA patients



stimulates arterial peripheral chemoreceptors, leading to increased minute ventilation (fast and deep breathing), subsequent episodes of acute lowering of heart rate (HR) and attenuation of adrenergic activity followed by a marked increase in HR and MSNA at the end of the period of hypoxia during apnoeic episodes (36) (Figure 16.2). Chronic potentiated activation of arterial chemoreflexes as a result of recurrent events of oxygen desaturation appears to be the leading contributor for persistently elevated sympathetic nerve activity to the skeletal muscle (36,37).

Studies using microneurography consistently confirmed that human obesity is associated with increased sympathetic activation (38). However, obese subjects with sleep apnoea were found to demonstrate extremely elevated levels of MSNA ( $61 \pm 8$  bursts per 100 heartbeats) when compared to obese subjects without sleep apnoea ( $42 \pm 3$  bursts per 100 heartbeats) or normal-weight subjects ( $41 \pm 3$  bursts per 100 heartbeats) (39), as indicated in Figure 16.3. These findings indicate that obesity alone, in the absence of OSA, is not accompanied by increased sympathetic outflow to the skeletal muscle vascular bed. Accordingly, unrecognized OSA in obese patients may play a critical role in triggering metabolic derangements and potentiating further associated CV risk. Augmented sympathetic activation in OSA patients that is independent of body weight but additive to that

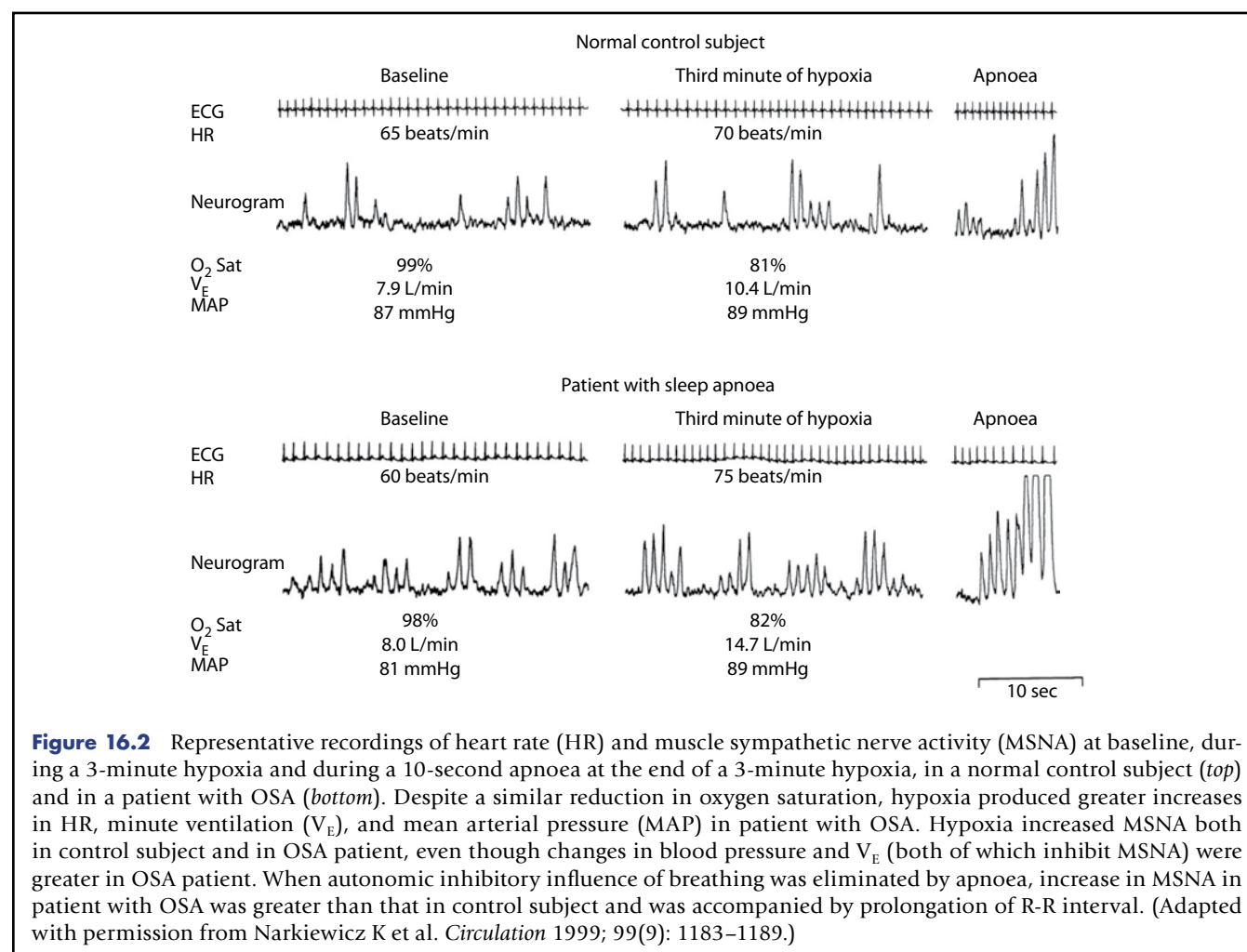
displayed by the overweight state has also been confirmed by other findings (40).

Moreover, altered sympathetic CV variability evident in OSA patients, even in the absence of other comorbidities (41), is likely to increase with the severity of OSA, thereby triggering OSA-related acute CV events (i.e. cardiac arrhythmia, sudden cardiac death, ischaemic heart disease, stroke, heart failure). Impaired CV reactivity during exercise and resultant reduced physical working capacity is a further important mechanism through which OSA leads to obesity (42).

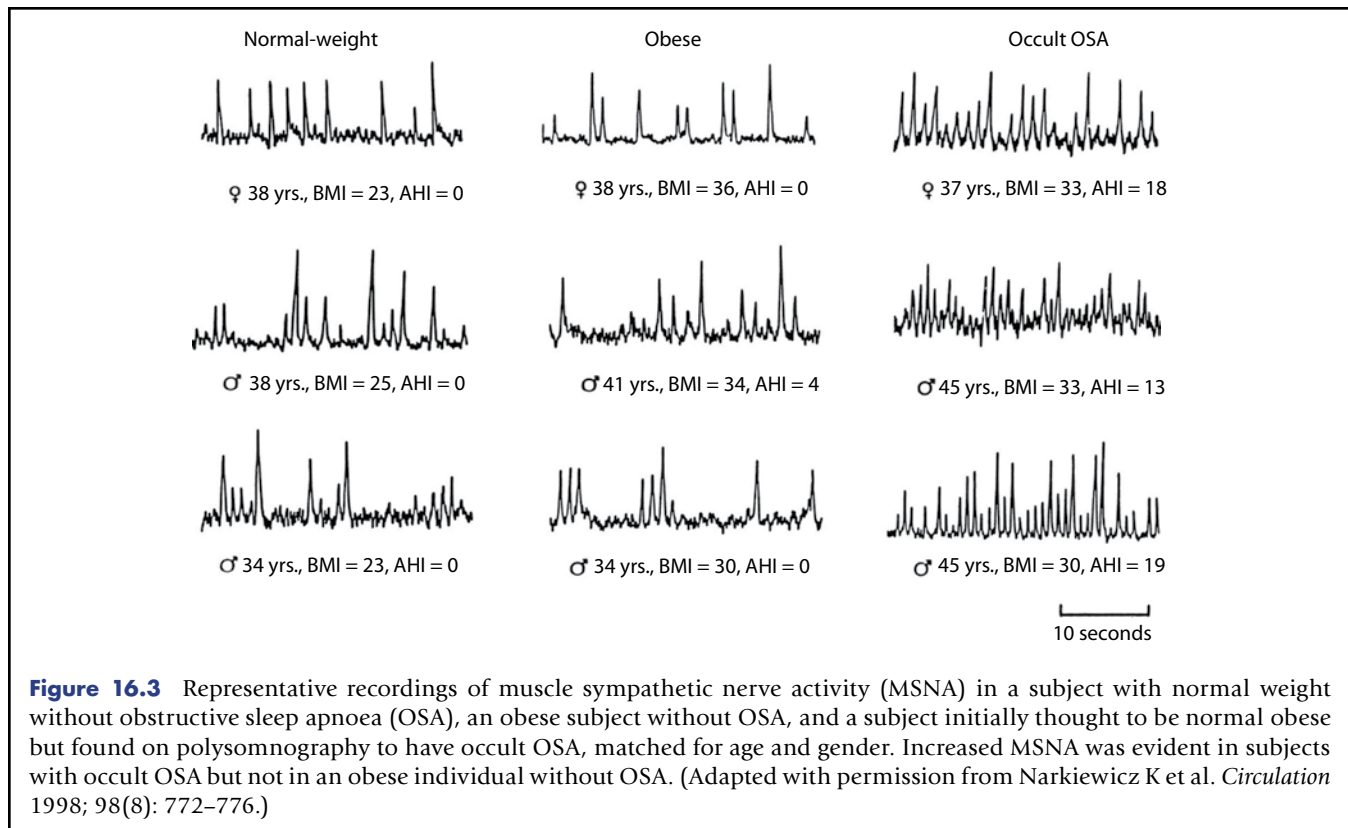
## METABOLIC DISTURBANCES

Patients with sleep apnoea commonly display higher levels of the adipose tissue-derived hormone, leptin, inflammatory markers, fasting plasma glucose, insulin and insulin resistance-producing cytokines (i.e. tumour necrosis factor- $\alpha$ , interleukin-6 etc.) when compared to BMI-matched controls without sleep apnoea who demonstrate intermediate values, or lean subjects with the lowest values (25).

Although excess adiposity is the major indicator of insulin resistance, not all overweight or obese individuals are insulin resistant (43). Studies in sleep apnoea patients







have documented that sleep-disordered breathing parameters including AHI and minimum oxygen saturation are independent determinants of insulin resistance (44). Consequently, the association between OSA and insulin resistance remained significant in both obese and non-obese subjects (44). The independent relationship between sleep-disordered breathing and metabolic dysfunction has been also confirmed by the results of the Sleep Heart Health Study (45). Sleep-disordered breathing has been associated with glucose intolerance and insulin resistance independently of BMI, waist circumference, age, gender, smoking and sleep duration. The severity of OSA, as determined by the RDI, has been associated with the degree of insulin resistance, whereas sleep-related hypoxemia has been linked to both glucose intolerance and insulin resistance (45). While the mechanistic pathways were not directly indicated in this study, it is likely that sympathetic activation underlying OSA-related hypoxemia importantly contributes to metabolic abnormalities and subsequent risk of type 2 diabetes.

## ROLE OF LEPTIN AND GHRELIN IN OSA

Leptin and ghrelin are the two important hormones involved in the regulation of energy balance and body weight in humans (46). Leptin, predominantly produced by adipose tissue, acts through the receptors located in the hypothalamus and inhibits feeding, increases sympathetic activation and promotes inflammation. The action of leptin is opposed by the hormone ghrelin produced by the gastrointestinal tract acting on the hypothalamic brain

cells to increase appetite, and influences energy homeostasis. The circulating level of leptin directly correlates with BMI and has been found to be paradoxically increased in obese subjects causing the phenomena known as leptin resistance (similar to insulin resistance) through various mechanisms including modulation of the leptin receptor–signalling pathway (47). Plasma ghrelin is inversely related to body weight, with decreased levels in obesity and increased concentration following weight loss (46).

A large variation in serum leptin levels has been documented in OSA patients including higher, unchanged or lower leptin concentrations (48). Most studies have reported higher leptin values in OSA subjects independent of BMI. Compared to subjects with a similar BMI but without sleep-disordered breathing, OSA subjects had higher circulating leptin levels which positively correlated with BMI, skinfold thickness, serum cholesterol, low-density lipoprotein cholesterol, insulin, insulin/glucose ratio, AHI and oxygen desaturation time (49). Another study which included male subjects confirmed higher leptin values in both moderate-to-severe and severe OSA compared to matched BMI controls (50). Interestingly, in this study the percentage of total sleep time spent with hypoxemia (saturation <90%) was found to be a significant predictor for leptin levels independent of obesity (50). While the mechanisms underlying the association between nocturnal hypoxemia and hyperleptinemia were not addressed in this study, the sympathetic activation seems to play a critical underlying role in this scenario. Interestingly, elevated plasma leptin and MSNA levels have been demonstrated in newly diagnosed healthy patients with untreated sleep apnoea compared to similarly obese control subjects without sleep apnoea (51). Higher leptin levels in OSA

independent of body fat content suggest that OSA is associated with greater resistance to the action of leptin and predisposition to weight as compared to similarly obese individuals without sleep apnoea (51).

Further, findings from experimental studies have demonstrated that chronic intermittent hypoxia induces changes in leptin and leptin-signalling protein within the carotid bodies, thereby possibly altering chemoreflex sensitivity (52). Hyperleptinemia alone potentiates sympathoexcitatory responses during the reflex activation of arterial chemoreceptors (53) and exaggerates the hypoxic CV responses through the activation of the chemoreflexes (54).

Another study in a male patient cohort with OSA documented a higher fasting leptin and ghrelin levels compared to BMI-matched controls without OSA (55). This study found that a 2-day treatment with continuous positive airway pressure (CPAP) decreased plasma ghrelin in almost all OSA patients to the levels that were only slightly higher compared to that in controls ( $n = 9$ ). While a 2-day therapy resulted in no changes in leptin levels, an 8-week CPAP treatment produced a significant reduction in leptin levels without an effect on BMI (55). These findings indicate that elevated leptin and ghrelin levels evident in OSA subjects are not determined by obesity alone (55).

It should be noted that not all studies found increased leptin and ghrelin levels in OSA patients. Significantly higher serum leptin levels were found in OSA patients compared to controls but without significant differences in serum ghrelin levels between OSA patients and controls. Serum leptin levels were significantly correlated with BMI in both OSA patients and controls, but only in OSA patients was leptin associated with AHI (56). Another study found significantly higher serum ghrelin levels in an OSAS group compared to the control group. Ghrelin levels were associated with AHI and the ESS score in OSA only but there were no significant differences noted in the levels of leptin, adiponectin and resistin between groups (57).

Despite these controversial results, leptin has been proposed to be a prognostic marker of OSA. This is supported by the findings from studies documenting reversibility of hyperleptinemia following therapy with nasal CPAP (nCPAP). A significant decrease in circulating leptin levels was achieved with 6 months of therapy with nCPAP, indicating that hyperleptinemia in OSA cannot be explained entirely by increased adiposity (49).

## ROLE OF HYPOCRETIN IN OSA

Amongst numerous neurohormones, the hypocretin system (orexin-A) has been found to play an important role in the regulation of sleep and arousal states, feeding and energy balance, centrally mediated CV regulatory actions and other peripheral functions (58). The vast majority of studies documenting orexin deficiency come from patients demonstrating narcolepsy or primary hypersomnia (59). Given the presence of sleep disturbances (i.e. daytime sleepiness, wakefulness) in OSA patients, it has been suggested that orexin may be implicated in the pathogenesis of disease. Previous studies documented low levels of orexin-A in OSA patients (60–62), which decrease in parallel with the severity of disease (60). Abnormally low orexin-A levels have been found in untreated patients with severe OSA (mean AHI  $54 \pm 4$  events per hour) when

compared to healthy controls (61). Treatment of the OSA cohort with CPAP for at least 1 year also resulted in lower values of orexin-A compared to healthy controls (61). A reduced orexin-A level appeared to be independent of the number of apnoeas during sleep, the presence of daytime sleepiness or obesity (61).

Conversely, there is also evidence documenting higher orexin-A levels which correlated with the clinical severity of OSA and arousal index (63). In this study, 3 months' therapy with CPAP decreased orexin-A levels and the ESS score (63). Whether elevated plasma orexin levels reflect central manifestations of apnoea-hypopnea-related arousal is yet to be determined.

## THERAPEUTIC INTERVENTIONS

Treatment of OSA should be initiated with CPAP therapy based on technically adequate PSG or home sleep apnoea testing (8). Recently, a meta-analysis of seven randomized controlled trials ( $n = 4268$ ) of the use of CPAP therapy in the prevention of CV events in patients with OSA has demonstrated non-significant 26% relative risk reduction in major adverse CV events (MACE) (64). However, CPAP adherence time  $\geq 4$  hours per night reduced the risk of MACE by 57% with no beneficial effects on myocardial infarction, all-cause mortality, atrial fibrillation/flutter or heart failure. CPAP had a positive effect on mood and reduced the daytime sleepiness assessed by the ESS questionnaire (64).

The effect of CPAP therapy on body weight remains unclear, with studies reporting no change or increases in BMI. A recent meta-analysis of 25 RCTs ( $n = 3181$ ) has indicated that OSA treatment with CPAP promotes significant increase in BMI and weight and that baseline weight was a predictor of increased BMI after CPAP (65). The increasing weight associated with OSA treatment was not influenced by age, gender, baseline BMI, baseline weight, OSA severity, differences in study design, and duration of follow-up, CPAP compliance, dieting or physical activity (65).

The bidirectional link between obesity and sleep-disordered breathing emphasizes that CPAP initiation to treat overweight and obese patients with OSA should be complemented by therapies for body weight reduction (i.e. lifestyle interventions). This is corroborated by the findings from the randomized controlled trial in which obese patients with moderate-to-severe OSA were assigned to receive CPAP therapy, a weight-loss intervention (dietary program) only, or both CPAP plus a weight-loss program for 24 weeks (66). Weight loss only and the combined interventions (CPAP plus weight loss) produced reductions in CRP levels, insulin resistance, and serum triglyceride levels. None of these changes were observed in patients receiving CPAP alone. No significant incremental effect on CRP levels was found for the combined interventions as compared with either weight loss or CPAP alone. The decline in body weight was comparable in the weight-loss and combined-intervention groups (6.8 and 7.0 kg, respectively), but no significant weight changes were noted in the CPAP group. In addition to improved metabolic parameters, this study found that the combined interventions resulted in a greater systolic BP reduction (14.1 mmHg) when compared to weight loss (6.8 mmHg) or CPAP (3.0 mmHg) alone at 24 weeks' follow-up among adherent subjects (66). While outcomes on OSA severity

were not reported in this study, the combined CPAP and weight loss dietary intervention was found to be a superior approach in improving CV risk profile to either therapy alone.

Of note, primary-led weight management (i.e. dietary program and/or physical activity) for prevention or remission of OSA is a practical clinical target for primary care.

For morbidly obese patients, in whom OSA is highly prevalent, bariatric surgery is the only available method for a sustained and long-term weight reduction. A systematic review of a total 69 studies ( $n = 13,900$ ) has demonstrated that bariatric surgery improves or resolves sleep apnoea in a majority of bariatric patients irrespective of the specific type of surgery (67).

## CONCLUSION

The increasing worldwide prevalence in overweight and obesity over the past few decades has triggered the incidence of sleep-disordered breathing. An increase in OSA awareness and associated CV risk is a global imperative for reducing the disease burden. Although CPAP is effective for treatment of OSA, it is essential to target obesity in order to properly address CV risk in this population. Weight loss is obviously beneficial in reducing cardio-metabolic consequences related to OSA and obesity. Low-cost, effective weight loss interventions are clearly warranted to halt the worldwide burden attributable to obesity.

## REFERENCES

- Narang I, Mathew JL. Childhood obesity and obstructive sleep apnea. *J Nutr Metab* 2012; 2012: 134202.
- Fleetham J, Ayas N, Bradley D et al. Canadian Thoracic Society guidelines: Diagnosis and treatment of sleep disordered breathing in adults. *Can Respir J* 2006; 13(7): 387–392.
- Strollo PJ Jr, Rogers RM. Obstructive sleep apnea. *N Engl J Med* 1996; 334(2): 99–104.
- Sert Kuniyoshi FH, Zellmer MR, Calvin AD et al. Diagnostic accuracy of the Berlin Questionnaire in detecting sleep-disordered breathing in patients with a recent myocardial infarction. *Chest* 2011; 140(5): 1192–1197.
- Margallo VS, Muxfeldt ES, Guimaraes GM, Salles GF. Diagnostic accuracy of the Berlin questionnaire in detecting obstructive sleep apnea in patients with resistant hypertension. *J Hypertens* 2014; 32(10): 2030–2036, discussion 2037.
- Ahmadi N, Chung SA, Gibbs A, Shapiro CM. The Berlin questionnaire for sleep apnea in a sleep clinic population: Relationship to polysomnographic measurement of respiratory disturbance. *Sleep Breath* 2008; 12(1): 39–45.
- Cowan DC, Allardice G, Macfarlane D et al. Predicting sleep disordered breathing in outpatients with suspected OSA. *BMJ Open* 2014; 4(4): e004519.
- Kapur VK, Auckley DH, Chowdhuri S et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med* 2017; 13(3): 479–504.
- Chung F, Subramanyam R, Liao P et al. High STOP-Bang score indicates a high probability of obstructive sleep apnoea. *Br J Anaesth* 2012; 108(5): 768–775.
- Chung F, Chau E, Yang Y et al. Serum bicarbonate level improves specificity of STOP-Bang screening for obstructive sleep apnea. *Chest* 2013; 143(5): 1284–1293.
- Nagappa M, Liao P, Wong J et al. Validation of the STOP-Bang Questionnaire as a screening tool for obstructive sleep apnea among different populations: A systematic review and meta-analysis. *PLOS ONE* 2015; 10(12): e0143697.
- American Academy of Sleep Medicine. *The International Classification of Sleep Disorders*. 3rd ed (ICSD-3). Darien, IL; 2014.
- Penzel T, Schobel C, Fietze I. Revise respiratory event criteria or revise severity thresholds for sleep apnea definition? *J Clin Sleep Med* 2015; 11(12): 1357–1359.
- Duce B, Milosavljevic J, Hukins C. The 2012 AASM respiratory event criteria increase the incidence of hypopneas in an adult sleep center population. *J Clin Sleep Med* 2015; 11(12): 1425–1431.
- Arnardottir ES, Bjornsdottir E, Olafsdottir KA et al. Obstructive sleep apnoea in the general population: Highly prevalent but minimal symptoms. *Eur Respir J* 2016; 47(1): 194–202.
- Costa LE, Uchoa CH, Harmon RR et al. Potential underdiagnosis of obstructive sleep apnoea in the cardiology outpatient setting. *Heart* 2015; 101(16): 1288–1292.
- Peppard PE, Young T, Barnett JH et al. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013; 177(9): 1006–1014.
- Senaratna CV, Perret JL, Lodge CJ et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Med Rev* 2017; 34: 70–81.
- Peppard PE, Young T, Palta M et al. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA* 2000; 284(23): 3015–3021.
- Newman AB, Foster G, Givelber R et al. Progression and regression of sleep-disordered breathing with changes in weight: The Sleep Heart Health Study. *Arch Intern Med* 2005; 165(20): 2408–2413.
- Tufik S, Santos-Silva R, Taddei JA, Bittencourt LR. Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. *Sleep Med* 2010; 11(5): 441–446.
- Resta O, Foschino-Barbaro MP, Legari G et al. Sleep-related breathing disorders, loud snoring and excessive daytime sleepiness in obese subjects. *Int J Obes Relat Metab Disord* 2001; 25(5): 669–675.
- Lopez PP, Stefan B, Schulman CI, Byers PM. Prevalence of sleep apnea in morbidly obese patients who presented for weight loss surgery evaluation: More evidence for routine screening for obstructive sleep apnea before weight loss surgery. *Am Surg* 2008; 74(9): 834–838.
- Kositarnit W, Muntham D, Udomsawaengsup S, Chirakalwasan N. Prevalence and associated factors of obstructive sleep apnea in morbidly obese patients undergoing bariatric surgery. *Sleep Breath* 2017; 22(1): 251–256.
- Vgontzas AN, Papanicolaou DA, Bixler EO et al. Sleep apnea and daytime sleepiness and fatigue: Relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab* 2000; 85(3): 1151–1158.
- Schafer H, Pauleit D, Sudhop T et al. Body fat distribution, serum leptin, and cardiovascular risk factors in men with obstructive sleep apnea. *Chest* 2002; 122(3): 829–839.
- Bjorntorp P. Metabolic implications of body fat distribution. *Diabetes Care* 1991; 14(12): 1132–1143.
- Phillips BG, Hisel TM, Kato M et al. Recent weight gain in patients with newly diagnosed obstructive sleep apnea. *J Hypertens* 1999; 17(9): 1297–1300.
- Basta M, Lin HM, Pejovic S et al. Lack of regular exercise, depression, and degree of apnea are predictors of excessive daytime sleepiness in patients with sleep apnea: Sex differences. *J Clin Sleep Med* 2008; 4(1): 19–25.
- Patel SR, Blackwell T, Redline S et al. The association between sleep duration and obesity in older adults. *Int J Obesity* 2008; 32(12): 1825–1834.
- Beccuti G, Pannain S. Sleep and obesity. *Curr Opin Clin Nutr Metab Care* 2011; 14(4): 402–412.
- Benedict C, Brooks SJ, O'Daly OG et al. Acute sleep deprivation enhances the brain's response to hedonic food stimuli: An fMRI study. *J Clin Endocrinol Metab* 2012; 97(3): E443–E447.
- Somers VK, White DP, Amin R et al. Sleep apnea and cardiovascular disease: An American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation* 2008; 118(10): 1080–1111.
- Molnar MZ, Mucsi I, Novak M et al. Association of incident obstructive sleep apnoea with outcomes in a large cohort of US veterans. *Thorax* 2015; 70(9): 888–895.
- Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 1995; 96(4): 1897–1904.

36. Narkiewicz K, van de Borne PJ, Pesek CA et al. Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea. *Circulation* 1999; 99(9): 1183–1189.
37. Narkiewicz K, van de Borne PJ, Montano N et al. Contribution of tonic chemoreflex activation to sympathetic activity and blood pressure in patients with obstructive sleep apnea. *Circulation* 1998; 97(10): 943–945.
38. Narkiewicz K, Grassi G, Mancia G, Hedner T. *The Sympathetic Nervous System and Cardiovascular Disease*. Via Medica Gdansk, Gdańsk; 2008.
39. Narkiewicz K, van de Borne PJ, Cooley RL et al. Sympathetic activity in obese subjects with and without obstructive sleep apnea. *Circulation* 1998; 98(8): 772–776.
40. Grassi G, Facchini A, Trevano FQ et al. Obstructive sleep apnea-dependent and -independent adrenergic activation in obesity. *Hypertension* 2005; 46(2): 321–325.
41. Narkiewicz K, Montano N, Cogliati C et al. Altered cardiovascular variability in obstructive sleep apnea. *Circulation* 1998; 98(11): 1071–1077.
42. Grote L, Hedner J, Peter JH. The heart rate response to exercise is blunted in patients with sleep-related breathing disorder. *Cardiology* 2004; 102(2): 93–99.
43. Reaven G. All obese individuals are not created equal: Insulin resistance is the major determinant of cardiovascular disease in overweight/obese individuals. *Diab Vasc Dis Res* 2005; 2(3): 105–112.
44. Ip MS, Lam B, Ng MM et al. Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med* 2002; 165(5): 670–676.
45. Punjabi NM, Shahar E, Redline S et al. Sleep-disordered breathing, glucose intolerance, and insulin resistance: The Sleep Heart Health Study. *Am J Epidemiol* 2004; 160(6): 521–530.
46. Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: A review. *Obes Rev* 2007; 8(1): 21–34.
47. Myers MG, Cowley MA, Munzberg H. Mechanisms of leptin action and leptin resistance. *Annu Rev Physiol* 2008; 70: 537–556.
48. Pan W, Kastin AJ. Leptin: A biomarker for sleep disorders? *Sleep Med Rev* 2014; 18(3): 283–290.
49. Ip MS, Lam KS, Ho C et al. Serum leptin and vascular risk factors in obstructive sleep apnea. *Chest* 2000; 118(3): 580–586.
50. Kapsimalis F, Varouchakis G, Manousaki A et al. Association of sleep apnea severity and obesity with insulin resistance, C-reactive protein, and leptin levels in male patients with obstructive sleep apnea. *Lung* 2008; 186(4): 209–217.
51. Phillips BG, Kato M, Narkiewicz K et al. Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea. *Am J Physiol Heart Circ Physiol* 2000; 279(1): H234–H237.
52. Messenger SA, Moreau JM, Ciriello J. Effect of chronic intermittent hypoxia on leptin and leptin receptor protein expression in the carotid body. *Brain Res* 2013; 1513: 51–60.
53. Ciriello J, Moreau JM. Systemic administration of leptin potentiates the response of neurons in the nucleus of the solitary tract to chemoreceptor activation in the rat. *Neuroscience* 2013; 229: 88–99.
54. Polotsky Y, Shin M, Caballero C et al. Leptin signals in the carotid body to up-regulate the hypoxic chemoreflex and induce hypertension. *Eur Respir J* 2016; 48: OA1801.
55. Harsch IA, Konturek PC, Koebsnick C et al. Leptin and ghrelin levels in patients with obstructive sleep apnoea: Effect of CPAP treatment. *Eur Respir J* 2003; 22(2): 251–OA1257.
56. Ulukavak Ciftci T, Kokturk O, Bukan N, Bilgihan A. Leptin and ghrelin levels in patients with obstructive sleep apnea syndrome. *Respiration* 2005; 72(4): 395–401.
57. Ursavas A, Ilcol YO, Nalci N et al. Ghrelin, leptin, adiponectin, and resistin levels in sleep apnea syndrome: Role of obesity. *Ann Thorac Med* 2010; 5(3): 161–165.
58. Ebrahim IO, Howard RS, Kopelman MD et al. The hypocretin/orexin system. *J R Soc Med* 2002; 95(5): 227–230.
59. Ebrahim IO, Sharief MK, de Lacy S et al. Hypocretin (orexin) deficiency in narcolepsy and primary hypersomnia. *J Neurol Neurosurg Psychiatry* 2003; 74(1): 127–130.
60. Nishijima T, Sakurai S, Arihara Z, Takahashi K. Plasma orexin-A-like immunoreactivity in patients with sleep apnea hypopnea syndrome. *Peptides* 2003; 24(3): 407–411.
61. Busquets X, Barbe F, Barcelo A et al. Decreased plasma levels of orexin-A in sleep apnea. *Respiration* 2004; 71(6): 575–579.
62. Sakurai S, Nishijima T, Takahashi S et al. Clinical significance of daytime plasma orexin-A-like immunoreactivity concentrations in patients with obstructive sleep apnea hypopnea syndrome. *Respiration* 2004; 71(4): 380–384.
63. Igarashi N, Tatsumi K, Nakamura A et al. Plasma orexin-A levels in obstructive sleep apnea-hypopnea syndrome. *Chest* 2003; 124(4): 1381–1385.
64. Khan SU, Duran CA, Rahman H et al. A meta-analysis of continuous positive airway pressure therapy in prevention of cardiovascular events in patients with obstructive sleep apnoea. *Eur Heart J* 2017.
65. Drager LF, Brunoni AR, Jenner R et al. Effects of CPAP on body weight in patients with obstructive sleep apnoea: A meta-analysis of randomised trials. *Thorax* 2015; 70(3): 258–264.
66. Chirinos JA, Gurubhagavatula I, Teff K et al. CPAP, weight loss, or both for obstructive sleep apnea. *N Engl J Med* 2014; 370(24): 2265–2275.
67. Sarkhosh K, Switzer NJ, El-Hadi M et al. The impact of bariatric surgery on obstructive sleep apnea: A systematic review. *Obes Surg* 2013; 23(3): 414–423.



# THE METABOLIC SYNDROME IN HYPERTENSION

# 17

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## INTRODUCTION

High blood pressure is a common feature of a constellation of anthropometric and metabolic abnormalities that include abdominal obesity, insulin resistance (IR) and dyslipidemia, characterized by low levels of high-density lipoprotein cholesterol and high levels of triglycerides. This cluster of clinical, hemodynamic and metabolic conditions has been observed simultaneously to a greater degree than one would expect by chance alone, supporting the existence of a discrete disorder, the so-called metabolic syndrome (MS). Several criteria have been proposed for the definition of MS; however, from a clinical point of view, the most useful diagnostic criteria are those based on criteria that can easily be assessed in daily practise.

According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) (1) and the American Heart Association/National Heart Blood and Lung Institute) (AHA/NHLBI) (2), the diagnostic criteria for MS are based on measures of abdominal circumference, lipid metabolism, plasma glucose and blood pressure (BP) (Table 17.1). The diagnosis of MS is established when three or more of the cardiovascular risk factors listed in Table 17.1 are present. In contrast, the International Diabetes Federation (IDF) (3) suggests that central obesity and insulin resistance are the most important causative factors for the development of MS. Central (abdominal) obesity is considered as a prerequisite component for the diagnosis of MS, and measurement of waist circumference is recommended for its identification, given the fact that waist circumference measurement is a simple procedure and its value is independently associated with each MS component, including insulin resistance (4,5).

In 2009, an expert panel of the major scientific associations agreed on harmonized definition criteria for MS (6). The main conclusions of this joint interim statement included that there should not be a single obligatory component for the diagnosis of MS. Three out of the five findings stated in Table 17.1 would qualify an individual for MS. In addition, a single set of cutoff points was established for all components of MS except for large waist circumference, where the use of national or regional cutoff points is recommended (6). The establishment of global gender- and ethnic-specific thresholds of normal waist

circumference is challenging due to differences in the relation of abdominal obesity to other metabolic risk factors and differences in the predictive value of various levels of abdominal obesity for cardiovascular disease (CVD) and diabetes (7).

The Joint Statement further considered more sophisticated measurements of lipid alterations in order to identify individuals with so-called atherogenic dyslipidemia. The term *atherogenic dyslipidemia* describes the combination of increased serum triglycerides, apolipoprotein B (ApoB), and small low-density lipoprotein (LDL) particles together with low levels of high-density lipoprotein (HDL)-cholesterol. This aggregation of lipoprotein abnormalities is highly atherogenic (8) and is commonly observed in patients with both type 2 diabetes and MS.

Some authors and scientific societies claimed that the MS is not a single pathophysiological entity and criticized the lack of a clear definition (9–11). In addition, current definitions of MS do not take into account cardiovascular (CV) risk factors other than those traditionally used to define MS, including age, gender and smoking status (12). Although the causes and mechanisms of MS may indeed be diversified, there is controversy about whether the overall CV risk accompanying this condition may or may not be greater than the sum of its identifiable components (13,14). However, the simple and easy identification of MS components favours its use in clinical practise, ultimately helping the implementation of CV prevention strategies.

Over the past several decades, the role of uric acid in the development and progression of MS has been a matter of debate. Available evidence has shown that hyperuricaemia stimulates inflammation and causes metabolic, vascular and renal pathologies (15,16).

Numerous epidemiological studies observed a direct correlation between serum uric acid concentrations and the prevalence of MS components in both adults and children (17–19). Elevated uric acid levels further have been found to increase the risk of type 2 diabetes and hypertension (20–25). Ultimately, elevated uric acid levels conferred an increased cardiovascular risk, and uric acid-lowering therapies improved clinical outcomes (26–30). Although current definitions of MS do not take into account the presence of hyperuricemia, it is nowadays accepted that



**Table 17.1** Criteria for diagnosing the metabolic syndrome according the Adult Treatment Panel (ATP) III; the International Diabetes Federation (IDF) and the American Heart Association (AHA)

|            | Principal criteria | Abdominal obesity                 | Glucose mg/dL                           | HDL mg/dL                                                                 | Triglic mg/dL                           | BP mmHg                    |
|------------|--------------------|-----------------------------------|-----------------------------------------|---------------------------------------------------------------------------|-----------------------------------------|----------------------------|
| ATPIII (1) |                    | M $\geq$ 102 cm<br>W $\geq$ 88 cm | $\geq$ 110 <sup>a</sup><br>(6.1 mmol/L) | M $\leq$ 40<br>(1.03 mmol/L)<br>W $\leq$ 50<br>(1.29 mmol/L)              | $\geq$ 150<br>(1.7 mmol/L)              | $\geq$ 135/85 <sup>a</sup> |
| AHA (2)    |                    | M $\geq$ 94 cm<br>W $\geq$ 80 cm  | $\geq$ 100 <sup>a</sup><br>(5.6 mmol/L) | M $\leq$ 40<br>(1.03 mmol/L)<br>W $\leq$ 50 <sup>a</sup><br>(1.29 mmol/L) | $\geq$ 150 <sup>a</sup><br>(1.7 mmol/L) | $\geq$ 135/85 <sup>a</sup> |
| IDF (3)    | Central obesity    | M $\geq$ 94 cm<br>W $\geq$ 80 cm  | $\geq$ 100 <sup>a</sup><br>(5.6 mmol/L) | M $\leq$ 40<br>(1.03 mmol/L)<br>W $\leq$ 50 <sup>a</sup><br>(1.29 mmol/L) | $\geq$ 150 <sup>a</sup><br>(1.7 mmol/L) | $\geq$ 135/85 <sup>a</sup> |

Note: Diagnosis of metabolic syndrome is based on: (a) principal criteria plus at least two other; (b) in those without principal criteria, at least three.

<sup>a</sup> or in treatment for.

Abbreviations: M, men; W, women.

uric acid is an active participant in a complex network of pathological processes.

MS is a common condition globally, and can be found in approximately one-third of patients with essential hypertension. Importantly, MS considerably increases the risk of CV and renal events even in absence of overt diabetes. In this chapter, the prevalence, mechanisms, prognostic significance and treatment of MS in hypertensive patients are reviewed.

## PREVALENCE OF MS

Over the past several decades, the global prevalence of MS has increased dramatically. In the US, data from the National Health and Nutrition Examination Survey (NHANES) showed that the prevalence of MS in adults increased from 25.3% in 1988–1994 to 34.2% in 2007–2012 (31). A similar trend can be observed in all population subgroups independent of gender and ethnic background, as well as in children and adolescents (32–35). In the past 5–10 years, the prevalence of MS remained stable and followed demographic trends of obesity. A greater awareness of MS-related health consequences and a stricter control of MS components including hypertension and diabetes may contribute to the stabilizing prevalence of MS in recent years.

In Europe, a considerable variation in the prevalence of obesity and MS has been observed. The age-standardized percentage of men and women with MS ranges from 42.7% to 24%, respectively, in Southern European cohorts up to 78.2%, and 64.8% in Northern European cohorts (36). The variation in MS prevalence observed in different study populations can largely be explained by differences in characteristics of the study populations and the use of different criteria for the definition of MS (37–39). It is known that gender has a large impact on the estimation of MS prevalence, and an equal, higher or lower prevalence of MS in men compared to women has been reported (39–43). In addition, MS is strongly related to age. Approximately half of individuals aged 60 years or older fulfils current criteria

of MS in developed countries (44). A further increase in MS prevalence can be expected in the future due to the demographic trend of increasing age. MS is much more common in subjects with diabetes than in the general population, with reported rates that approximate 80–90% (45,46). In populations with low socioeconomic status, MS is further becoming an emerging epidemic due to several factors, including urbanization, lifestyle alterations (diet and exercise), economic influences, and increased life expectancy (47).

Among individuals with essential hypertension, the prevalence of MS is higher than in the general population (48–54). Hypertensives have an increased risk of developing MS and vice versa: MS components have been found to predict the incidence of hypertension (55,56). In addition, BP control is closely related to MS criteria: A higher prevalence of MS has been reported among uncontrolled hypertensives as compared to hypertensives with BP levels below target levels (48). Moreover, the risk of uncontrolled hypertension increases with the number of MS components (57). These findings suggest a reduced efficacy of antihypertensive treatment in subjects characterized by an adverse cardiometabolic profile that might be attributed to a more pronounced subclinical target-organ damage in these patients.

## ELEVATED BP AS A KEY COMPONENT OF MS

Hypertension is frequent in MS, and overall elevated BP, which represents one of the five components that lead to the identification of this condition. The prevalence of hypertension in MS can increase if the new threshold of 130/80 mmHg, proposed by the AHA guidelines, is used (58). In the PAMELA population study, for example, a blood pressure in the high normal or frankly hypertension range was found in more than 80% of the individuals with MS, followed in decreasing order of prevalence by visceral obesity, lipid abnormalities and impaired fasting glucose.

The high prevalence of BP abnormalities in MS explains the frequent occurrence of subclinical organ damage of the type that is frequently associated with and dependent on a BP elevation, such as left ventricular hypertrophy, arterial stiffening and increased urinary protein excretion (59). Some of these types of organ damage, however, also show an increased prevalence in individuals who have an MS without BP elevation to the hypertensive levels, suggesting that other components of this condition play a role independently on BP.

In a pooled analysis of prospective atherosclerosis progression/regression intra vascular ultra sound (IVUS) trials that included 3459 patients with established coronary artery disease, MS and its component risk factors were associated with plaque progression (60). MS was highly prevalent (57.8%) in this cohort and was associated with higher rates of disease progression. However, multivariable analysis showed that the excess plaque progression appeared to be driven more by its individual risk factors. Although each of the components predicted greater disease progression, hypertriglyceridemia and elevated body mass index (BMI) had the highest hazard ratios for atheroma progression. There were no significant differences for the risk of atherosclerosis progression in those patients with MS with or without high blood pressure or hypertension. Moreover, to have BP  $\geq 130/85$  mmHg or the use of medication was not significantly associated with disease progression in a multivariable model adjusting for age, sex, race, baseline LDL-C level and baseline statin use, with or without considering MS (51).

## MECHANISMS OF MS

MS is probably the result of multiple interactions among a large number of interconnected mechanisms. The precise sequence of events in MS is largely unknown but they eventually lead to an increase in cardiovascular and renal risk, and to the development of diabetes. The close relationships among the different components of the syndrome and their associated disturbances make it difficult to differentiate causes and consequences. Insulin resistance (IR) has been classically situated central in the origin of MS but it is probably the excess of caloric intake that leads to the various manifestations of the syndrome (61,62).

Mechanisms involved in MS are over-nutrition, excess of adipose tissue, IR and a constellation of independent factors, which include molecules of hepatic, vascular and immunologic origin with proinflammatory and procoagulant properties (61–63). Although IR is associated with obesity and central adipose tissue, not all obese subjects have IR. Those mechanisms controlling the expansion of the subcutaneous adipose tissue could be responsible for this observation (64,65). Skeletal muscle and the liver, not adipose tissue, are the two key insulin-response tissues involved in maintaining glucose balance, although abnormal insulin action in the adipocytes also plays a role in development of the syndrome (66).

At each of these key points, IR and obesity/proinflammatory molecules are probably modulated by demographics, lifestyle, and genetic, environmental and fetal factors (67). Superimposed upon these are infections and/or chronic exposure to certain drugs which can also contribute. The role of gut microbiota in MS is now receiving more attention, and certain food components, such as

dietary emulsifiers, can alter the microbiota and lead to an inflammatory state (68). The final individual phenotype probably results from complex interactions among all of the above-mentioned factors (2,69–71).

Altered function of adipose tissue, mainly in visceral fat, has been identified as a key driver, which precludes the development of the other features of MS, including impaired glucose homeostasis (72–74). The first structural event which follows from fat tissue increase is the infiltration of adipose tissue by bone marrow–derived macrophages in response to as-yet unknown signals (5,6,75,76). This is both a paracrine regulator of adipocyte function influencing free fatty acid (FFA) liberation and hormone secretion of leptin and adiponectin, as well as a source of the inflammatory mediators interleukin (IL)-6 and tumour-necrosis factor (TNF)- $\alpha$  released by adipose tissue. In addition to the structural changes, various functional abnormalities of adipose tissue–derived products have been described. These include an increase in FFA, leptin and cytokine release, and a reduction in adiponectin secretion. Age can also have a role in adipocyte dysfunction, and several genes associated with longevity such as *IGF-1* and *mTOR* could influence the adipocyte function (73,77).

A second key issue in the development of MS is *insulin resistance*. It is established in the skeletal muscle and the liver as a result of the inhibition of insulin-stimulated glucose transport activity mainly by accumulation of acyl CoA and diacylglycerol in the cytoplasm easy by a reduction in the mitochondrial oxidative capacity (78,79). This increases serine kinase activity, which leads to the suppression of insulin signalling by reducing IRS-2 and Glut-4 transport (80). There are several factors related to IR. Adipocytokines which are released from the adipose tissue seem to alter insulin sensitivity in the liver and muscle (81). The visceral adipose tissue could be considered as a surrogate marker for the accumulation of lipids at ectopic sites and of lipotoxicity, which would occur in parallel in the liver and muscle, causing IR in these tissues (81). Also, the excess of visceral fat may have direct diabetogenic properties. This theory would be supported by the increase of macrophages in this tissue that would release proinflammatory cytokines leading to IR. It is also possible that both the lipotoxicity in peripheral tissues and the production of cytokines by visceral fat could contribute to the systemic IR (81). IR and the consequent hyperinsulinemia have always been considered key elements in the development of MS, although IR is strongly associated with atherogenic dyslipidemia and inflammation, whereas its mechanistic link with other MS components, such as hypertension and a prothrombotic state (63,82), is less well established.

There is increasing evidence that aldosterone through genomic and nongenomic effects on the mineralocorticoid receptor (MR) may be related to insulin resistance, endothelial dysfunction and with other components of MS (83,84). The adipose tissue produces a lipid soluble factor that stimulates glucocorticoids and aldosterone secretion, and these hormones can promote the adipogenesis and inflammation in fat tissue. This unidentified lipid soluble factor could be leptin, which has recently been described as a direct regulator of the aldosterone synthase expression through calcium-dependent mechanisms (85–87). Several clinical studies support the potential benefit of MR antagonism in hypertensive patients with MS (88–90). This can be partly due to a reduction in the proinflammatory

adipokine levels, which are usually elevated in MS, such as TNF- $\alpha$ , MCP-1, and IL-6, together with an improvement in the expression of adiponectin (91,92).

## MECHANISMS OF ELEVATED BLOOD PRESSURE IN MS

Obesity and IR, two of the main components of MS, probably play an important role on the increment of BP and the development of hypertension (93). Although the precise mechanisms involved remain partially unresolved, factors such as overactivity of the sympathetic (94), stimulation of the renin-angiotensin systems (RAS) (7,95), abnormal renal sodium handling (96), and endothelial dysfunction (97,98) need to be considered (Figure 17.1).

*Abnormal sodium handling* has been postulated to be one of the main suspects for the development of hypertension in MS. It is known that not all obese or MS patients develop hypertension as it happens in the rodent model of MS or obesity (99,100). One potential explanation is the increase in salt sensitivity, which could be related to activation of the epithelial Na<sup>+</sup> channel (ENaC) by insulin or other factors (101). However, the chronic block of ENaC does not affect the BP, which means that other retentive Na pathways are probably involved (99).

Overactivity of the *sympathetic nervous system (SNS)* is mainly mediated by five physiopathological mechanisms: (1) hormones such as cortisol or aldosterone; (2) metabolic factors such as leptin, insulin or FFA; (3) reflex activation by baro- or chemoreceptors; (4) inflammation; and (5) endothelial or haematological factors may play an important role in the frequent association of MS with hypertension (93,102). A great deal of evidence supports the finding that obese individuals have increased levels of plasma norepinephrine, faster urine turnover of norepinephrine in peripheral tissues and increased muscle sympathetic activity, as measured directly by microneurographic methods (103–107). Long-term sympathetic activation in MS may raise BP through multiple mechanisms, including an increase in renal tubular sodium reabsorption (105),

systemic vasoconstriction and/or remodelling of the arterioles leading to an increase in their wall-to-lumen ratio and a consequent structural increment in vascular resistance (108). A short review focused on new information about the role of sympathetic nervous system in the MS has recently been published by Seravalle (102).

Together with the SNS, the activity of the RAS is increased in most obese individuals (109) despite the fact that obesity is accompanied by sodium retention and increased extracellular fluid volume, which should inactivate renin release from the kidney and angiotensin II formation. The cause of RAS activation may be due to enhanced renin production caused by diminished sodium delivery to the macula densa because of its greater reabsorption in the loop of Henle. This can be mediated by insulin, which can also activate the different enzymes of the system in vascular endothelial cells and therefore contribute to an increase in the levels of angiotensin II (110). A stimulation of renin release by the increased sympathetic nerve activity to the kidneys may also be involved (96,111). Finally, an increase of angiotensinogen formation in adipose tissue may contribute to RAS activation. Serum uric acid has long been associated with obesity, MS and hypertension, although its role as an independent cardiovascular risk factor has not yet been proved (112). Uric acid may induce hypertension (HTN) by different mechanisms, including kidney sodium retention by ENaC and activation of the RAAS system by increasing the angiotensinogen levels (113–117). Moreover, the inhibitors of the enzyme xanthine oxidase have demonstrated significant reduction in BP, at least in the early stages (118). Angiotensin II enhances tubular sodium reabsorption (119), increases peripheral arterial resistance (111) and stimulates the SNS (120).

The increase in aldosterone levels which has been seen in hypertensives with visceral obesity (121) is one of the potential links to obesity-associated hypertension. Moreover, aldosterone has been proposed as a biomarker for several components of MS and related organ damage even in general populations (122). Overproduction of aldosterone has been directed to the production of potent mineralocorticoid-releasing factors in fat tissue (85) as well as to the ability of oxidized derivatives of linoleic acid to induce aldosterone synthesis (123). Aldosterone may raise blood pressure in obesity also through an action on MRs located not only in the kidney but also in the vasculature and the brain. The sensitivity of MR not only to aldosterone but also to glucocorticoids seems to be increased, as well as the ability of the enzyme 11 $\beta$ -hydroxysteroid dehydrogenase type 2 (11 $\beta$ -HSD2) to convert cortisol into cortisone, which does not have mineralocorticoid activity (124).

Weight gain is associated with hypertension by several mechanisms, but mainly through abnormal kidney function. Obese patients usually show an increase in sodium reabsorption and an impaired *renal-pressure natriuresis* that lead to an increase in extracellular volume (124). As previously discussed, sympathetic activity, RAS activation, hyperaldosteronism and disturbances in hemodynamic and intrarenal physical forces are all involved (94,124). Although initially the sodium balance is maintained through an elevated BP and GFR, the result of long-term hyperfiltration finally leads to glomerulosclerosis, and contributes to the sodium dependency of the elevated BP values in more advanced stages (125). Another mechanism of obesity-related hypertension is related to the physical compression of the kidneys by the accumulation

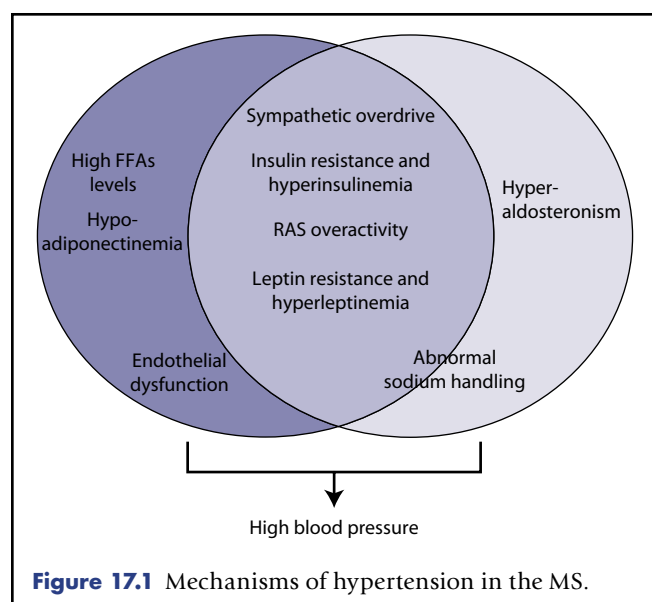


**Figure 17.1** Mechanisms of hypertension in the MS.

of visceral fat. This has shown to increase the interstitial hydrostatic pressure which can impair tubular flow and increase sodium reabsorption (124).

Various components of MS and also uric acid have an adverse impact on the *endothelium*, leading initially to oxidative stress, reduced nitric oxide (NO) bioavailability, endothelial dysfunction and vascular damage (116,126). Endothelial dysfunction is reflected by the presence of impaired endothelium-dependent vasodilatation as well as by the activation of inflammatory, proliferative and coagulation markers that are responsible for the proinflammatory and procoagulant states frequently seen in MS.

In this sense, one study, using a primate model of MS, supports the contribution of endothelial dysfunction for MS and its components (127). The animals selected for this study developed MS during the follow-up, so the authors were able to study this complex syndrome from its origin. Brachial flow-mediated dilatation (FMD) was clearly impaired in MS monkeys, which supports the idea that loss of endothelial reactivity is an early event in the progression of MS (127). Moreover, visceral obesity and hypertension could be key initial factors for the later development of the whole syndrome (127). This research was also able to demonstrate that the divergence between MS animals and controls was not only due to a difference in food or calorie intake, but that other factors such as genetics or metabolic predisposition could interact with environmental factors for the final phenotype (127).

The initial trigger for the development of endothelial dysfunction in MS is unknown, although several factors have been described. Insulin-resistant states are characterized by blunted insulin-mediated vasodilatation because of impairment of the phosphatidylinositol pathway (PI-3), which may lead to a decrease in the eNOS activity and the consequently lower NO production. The adverse consequences of these phenomena may be enhanced by the fact that since the MAP-kinase pathway is unaffected by insulin, there may be an unimpaired synthesis of endothelin 1 (ET-1), which favours vasoconstriction (128), vascular smooth muscle cell growth and cell migration from the vessel medial to the internal layer. This may promote an increase in vascular stiffness and thickness, favouring the cascade of events responsible for formation and progression of atherosclerotic plaque. Taken together, these phenomena may explain at least in part the increased BP and cardiovascular risk associated with hyperinsulinemia (129,130).

Low adiponectin levels also seem to induce endothelial dysfunction by the same pathway, through a PI-3 kinase-dependent mechanism (126). By this mechanism, adiponectin is able to increase the activity of eNOS, although other enzymes, such as 5' adenosine monophosphate-activated protein kinase (AMPK) or cyclooxygenase-2 (COX-2) have also been involved (126). Low plasma adiponectin levels have been shown to be associated with impaired endothelium-dependent vasodilatation (131–133), generating the hypothesis that hypo adiponectinemia contributes to the development of obesity-related hypertension via direct effect on the vasculature. Whether or not adiponectin supplementation may represent a potentially useful therapeutic modality in MS individuals with or without hypertension requires further study (132,134).

Some genetic variants that could be related to low adiponectin levels have been discovered in Asian hypertensive patients (135). One of these variants is located in an

intron region of the T-cadherin (*CDH13*) gene and has been further associated with an increased risk of MS (OR 1.42,  $p = 0.027$ ) (135). This gene encodes the cadherin-related superfamily of transmembrane proteins that mediate calcium-dependent intercellular adhesion. Both LDL and adiponectin can be specific ligands for T-cadherin, and its activation can further activate the nuclear factor- $\kappa$ B (NF- $\kappa$ B)-signalling pathway, which plays a central role in inflammation. The exact mechanisms by which this gene could be related to the appearance of MS in hypertension are not clearly understood. Other variants of this *CDH13* gene also seem to play a role in the development of MS, at least in women in northern Europe (136). Recently, certain genotypes of polymorphisms of the adiponectin gene have been associated with MS and low levels of adiponectin in adolescents from China (137). Although this study (137) has certain limitations, such as the cross-sectional design, the limited sample size and the fact that it probably cannot be applied to other ethnicities, it is clear that variants of this gene could modulate adiponectin levels, modifying the risk of developing hypertension and MS. It is hoped that these genetic results can help to identify genetic susceptibility to MS and associated traits.

Finally, plasma FFA elevation and also impaired endothelial-dependent vasodilatation FFA reduce the circulating levels of most amino acids, including L-arginine (i.e. the substrate for NO production) (133), and an inhibition of NO production by these compounds has been described. Acute short-lasting increases in FFA plasma level which follows a high lipid content meal induced transitory endothelial-dependent vasodilatation (138). It is not clear whether the association of FFA with hypertension is dependent on the presence of IR. For example, in the Japanese population-based Nagahama study (139), the authors found a favourable association of FFA levels with central BP, but it was not clear if these findings were related with the insulin-signalling pathways. In this sense, one small study comparing FFA levels among different groups with or without HTN and with or without IR did not find significant interaction between the presence of HTN and IR, therefore supporting an independent association of FFA with HTN (140).

## MS AND HYPERTENSION-INDUCED ORGAN DAMAGE

The prevalence of target-organ damage at different levels, including left ventricular hypertrophy (LVH), diastolic dysfunction, carotid atherosclerosis, arterial stiffness, retinopathy and microalbuminuria, is increased in hypertensive patients with MS when compared to those without it (52,59,141–148). Most of these types of organ damage are well-recognized surrogate endpoints, which may explain the association of MS with a higher risk of CV and renal events (142,147,149–153).

Several studies have demonstrated that MS is associated with a high prevalence of LVH in hypertensives, and that this is the case throughout a wide age spectrum. Moreover, MS by itself without hypertension has also been associated with greater left ventricular mass (LVM) and LVH (154). The number of MS components has been directly related to the risk of having electrocardiographic (EKG) (146) and echocardiographic LVH (51,52,155), although this has not



been confirmed in other studies (156,157). The effect of the MS on LV structure seems to be more pronounced and less dependent on hemodynamic factors in women than in men (59,156,158). However, the potential gender influence of MS for the development of LVH was not confirmed in other series (159). Atrial enlargement, a prognostic factor for the development of atrial fibrillation and stroke, has also been associated with MS and its components independently of LVM and geometry (156,160,161). Large prospective studies demonstrate an increased risk of new-onset atrial fibrillation (AF) in MS being the hazard ratio (HR) for hypertension greater than for the other components [HR = 1.69 (1.66–2.27)] (162). More recently, the REasons for Geographic and Racial Differences in Stroke [REGARDS] study (163) showed a significant association among the number of components of MS, each individual component including hypertension and MS itself with AF. Again, the largest adjusted HR [HR = 1.30 (1.19–1.41)] was for those individuals who had BP values  $\geq$  130/85 mmHg (163). This has been further observed in a more recent Swedish longitudinal study (164).

An increase in the prevalence of abnormal urinary albumin excretion has been observed among hypertensives with MS as compared to those without MS (51,52,160,165), and indeed microalbuminuria was considered a diagnostic element for MS in early definitions of this condition. The prevalence of microalbuminuria has been shown to increase with the number of MS components, a finding seen also in nondiabetic subjects and being fasting glucose and systolic blood pressure (SBP) the two components with major impact (51,166,167).

The relationship between MS and glomerular filtration rate (GFR) was studied in several population studies (165,168,169), although only few in hypertensives (148). In a cross-sectional survey of hypertensives seen in primary care, MS was associated with lower GFR, estimated by the Modification of Diet in Renal Disease formula (170). Furthermore, the number of MS components was linearly related to the prevalence of GFR  $<60$  mL/min/1.73 m<sup>2</sup> (171).

Meta-analysis of published studies seems to confirm the association of MS and its components with both microalbuminuria and a decrease in GFR being the risk associated with higher BP than for other components of MS [OR 1.61 (1.29–2.01)] (172,173). Interestingly, a large cross-sectional study, including more than 19,000 hypertensives, pointed out that serum uric acid could add synergically with MS to increase the risk of renal damage, but further studies are needed to confirm this observation (17).

MS and its components are also closely related to carotid atherosclerosis and intima-media thickness (IMT). The association between MS and carotid IMT has been observed in several studies (51,141,174), although to a weaker degree than that observed for markers of organ damage such as LVH and microalbuminuria. In a large survey of Japanese subjects, it was found that the prevalence of carotid atherosclerosis increased progressively with the number of MS components in hypertensives but not in normotensives (174).

Cuspidi et al., in a recent meta-analysis for the association of MS with subclinical carotid damage in the general population, further confirms the results from previous observations (175). The Metabolic syndrome and Artery Research (MARE) Consortium (11) was established to identify different clusters of MS components as well as sociocultural differences. Results for this collaboration demonstrate that not all the clusters seem to increase the

risk of extremely high IMT (defined as an IMT greater than percentile 95th). The risk to high IMT is greater when hypertension and abdominal obesity are present (176).

Pulse wave velocity (PWV) is greater in hypertensives with MS and has also been associated with a faster progression of aortic stiffness with age, independently of major individual CV risk factors, suggesting that it may promote premature vascular senescence (174,177). In the same way as for IMT, the MARE Consortium also showed that BP and abdominal obesity are the main contributors to an increase in PWV, the gold standard noninvasive method to determine arterial stiffness (178). Again, there seems to exist a relationship between the number of MS components and arterial stiffness, and when serum uric acid is elevated could also play an additional role (179).

## PROGNOSTIC VALUE OF MS IN HYPERTENSION

Whether MS increases CVD risk beyond its individual components is still a matter of controversy (6,10,145,153,180–182). Among the components of MS, central obesity, elevated BP and hyperglycaemia had the greatest risk for CVD [HR 2.36 (1.54–3.61)] and mortality [HR 3.09 (1.93–4.94)] in the Framingham Offspring Study (183). Only a limited number of studies seem to support that the presence of MS or its individual components worsens the prognosis in essential hypertension subjects.

In the Copenhagen Male Study (184), 2906 male participants were divided into three groups according to their fasting plasma triglyceride and HDL cholesterol levels, two lipid parameters highly related to IR and hyperinsulinemia. The CV risk was not increased in patients with hypertension in the absence of the above-defined dyslipidaemia. However, the group with high BP and dyslipidaemia was the one displaying the highest risk.

The prognostic significance of MS in hypertension was also analysed in the PIUMA cohort, which consisted of 1742 hypertensive patients without CV disease at entry. Over a 10.5-year follow-up, MS patients, as defined by the ATP III criteria, had a CV event rate that was almost double that of the patients without MS. In patients with MS, the CV risk remained greater after adjusting for age, gender, total plasma cholesterol serum, creatinine, smoking, LVH and 24-h systolic BP. The presence of MS was an independent predictor of both cardiac and cerebrovascular events, and the risk remained higher after removal of diabetic subjects (147).

In a Turkish study, 2225 men and women, free of CV disease at baseline and with a BP in the high-normal or hypertension range, were followed up for a mean of 4.1 years (185). Subjects defined as dyslipidemic hypertensives, based on BP, plasma triglycerides and HDL-cholesterol criteria for MS identification used by the National Cholesterol Education Program guidelines, had a higher CV risk as compared to hypertensives who did not have dyslipidaemia after adjustment for sex, age, LDL-cholesterol and smoking status. The dyslipidemic phenotype was associated with half of the attributable CV risk of the MS (185).

In the Hoorn study (186), 615 men and 749 women aged 50–75 years and without diabetes or a history of CV disease at baseline were followed over a 10-year period. With



prevalence of MS at baseline ranging from 17–32%, MS was associated with a higher CV risk, and the risk increased with the number of MS components. When the various MS definitions were compared, the ATP III definition was associated with about a twofold increase in the age-adjusted risk of fatal CV disease in men and nonfatal CV disease in women. For the World Health Organization (WHO), the European Group for the Study of Insulin (EGIR) and the American College of Endocrinology (ACE) definitions of MS, the hazard ratios per CV events were slightly lower.

The PAMELA study has provided further data on the association of MS with cardiac organ damage and increased cardiovascular risk (59). MS, as diagnosed using the 2003 ATP III criteria, was identified in 16.2% of 2051 individuals living in an urban population from northern Italy, with the prevalence increasing to about 25% in middle-aged and elderly subjects. The most and the least frequent MS components were high normal BP and impaired fasting glucose, respectively. Echocardiographically documented LV hypertrophy was seen more frequently in subjects with than in those without MS (20.6% vs. 10.6%), the difference occurring in males and females at all ages and after exclusion from either group of individuals with hypertension, as well as after adjustment of data for the 24-h mean systolic BP values. Over 148 months of follow-up, the risk of CV and all-cause death was significantly higher in MS individuals as compared with controls without MS even when adjusted by age, gender, and other cardiovascular risk factors (59).

A more recent Spanish study (187), performed in the general population aged more than 50 years and with a limited sample size, has tried to answer the question of whether diagnosis of MS helps to improve the prediction of CV events over its individual components or over the Framingham Risk Score (FRS). According to the results, the addition of MS as a dichotomic variable to FRS or to its individual components did not improve or worsen the prediction using a new index to evaluate a prediction tool such as the net reclassification improvement (NRI) (187).

## MANAGEMENT OF MS

The main objective of treatment of individuals with MS is to reduce the risk of cardiovascular or renal events and to prevent the development of type 2 diabetes or hypertension. In addition, treatment should prevent the progression (and favour the regression) of target-organ damage, which is commonly present in patients with MS. The ideal treatment strategy consists of the opposition of underlying pathophysiological mechanisms of MS. An effective reduction of visceral obesity, a hallmark of MS, is a desirable goal in the management of MS. Non-pharmacological strategies are based mainly on lifestyle interventions, including physical exercise and diet strategies. Despite the favourable cost-effectiveness of non-pharmacological MS management strategies, the implementation of these strategies rarely results in a long-lasting reduction in visceral fat and central obesity. However, every single MS component can successfully be improved with lifestyle and diet modifications, and current technologies such as mobile and Internet-based communication seem to increase the effectiveness of lifestyle change in MS patients (188).

Growing evidence shows that regular physical exercise has beneficial effects on the cardiometabolic profile of both healthy individuals and patients with MS. In a cohort of 3148 healthy adults followed over 6 years, improving the fitness status and reducing fat was associated with a reduction in the risk of developing HTN and MS (189). Cardiorespiratory fitness (CRF) further reduced the risk for systemic hypertension in a cohort including 3800 Korean men (189,190). Another large study including 53,772 men and 18,852 women found a significant association between CRF and both cardiovascular mortality and coronary heart disease (191).

In addition to an improvement in the cardiometabolic profile of patients with MS, physical exercise seems to be a key strategy for the prevention of MS. Large prospective cohort studies have shown that even modest exercise (less than 1 hour per week) was associated with a 30% lower risk of development of MS (192).

In general, a total of 150 minutes of exercise per week including a regimen of physical activity with moderate-to high-intensity exercise of 30-minute bouts on several days is recommended for BP and glycaemic management (193). The pathophysiological mechanisms underlying the potential benefit of exercise in MS are currently under investigation; however, changes in adipokine metabolism and reduction of the proinflammatory state seem to be key players (194,195).

In addition to physical exercise, the regular consumption of certain nutrients has been found to have an impact on BP and the metabolic profile of healthy individuals and patients with MS. The consumption of dark chocolate has been related to a reduction in BP and total cholesterol levels in several studies (196–198). Although the exact mechanisms are unknown, dark chocolate is rich in polyphenols, especially flavonoids, which produce vasodilation and decrease BP through the liberation of endothelial NO (199). Meta-analyses on the impact of flavanol-rich cocoa products on BP suggest beneficial effects, at least in hypertension and pre-hypertension (197,199–202). Moreover, some investigators have tried to model statistically the long-term effects and associated cost-effectiveness of dark chocolate intervention in a population with MS and hypertension (198). Ideally, dark chocolate consumption could potentially prevent 70 nonfatal and 15 fatal cardiovascular events per 10,000 population treated over 10 years. The estimated incremental cost effectiveness ratio was \$50,000 per years of life saved assuming that \$40 per person/year has been spent on a prevention strategy using dark chocolate.

Several trials have found that a diet enriched with nuts could be beneficial for MS management. Available evidence has shown that nut consumption is related to a reduction in the postprandial glycaemic response, a decrease in the risk of diabetes incidence in women, a cholesterol-lowering effect and a beneficial effect on BP and endothelial function (203). The protective effects of nut consumption on BP and metabolism can largely be explained by the modulation of inflammation and oxidation.

It has also been suggested that hypertensive patients with MS might be more susceptible to the adverse effects of salt intake as compared to hypertensives without MS (204). However, the potential role of reduced salt intake in the treatment of MS has not yet been clearly elucidated.

Regarding pharmacological strategies, the development of drugs that oppose IR or the metabolic hyperactivity that

**Table 17.2** Management recommendations for hypertension and metabolic syndrome (position statement of the ESH)

| MS component        | Threshold   | Goal         | Recommended                                                                                                                                                  | Observations                                                                                                                                                                                                                 |
|---------------------|-------------|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| High blood pressure | 130/85 mmHg | <130/80 mmHg | Non-pharmacologic treatment<br>Antihypertensive treatment:<br>First choice: ACEi or ARB<br>Second choice: CCB or<br>β-blockers with vasodilatory<br>activity | Thiazide-like diuretics should be avoided<br>in monotherapy or in high-dose<br>β-blockers should be avoided if not<br>compelling indication exists<br>Combination of thiazide diuretics plus<br>β-blockers should be avoided |

Source: Grundy SM et al. *Arterioscler Thromb Vasc Biol* 2004 February; 24(2): e19–e24.

may help body weight gain is promising, but the actual involvement of these drugs in MS is still unclear. The administration of pioglitazone, a peroxisome proliferator-activated receptor  $\gamma$  agonist, led to normalization of metabolic parameters and complete restoration of endothelial function in primate models with MS (127). Another promising candidate for the causal treatment of MS is molecules that interfere with the metabolism of epoxyeicosatrienoic acids (EETs). EETs have several beneficial properties including anti-inflammatory, antihypertensive and pro-proliferative effects. Cytochrome P450 (CYP2J3) epoxygenases metabolize arachidonic acid into EETs. A study conducted in rodents aimed to assess the effects of CYP2J3 gene delivery on insulin resistance and diabetes in fructose-induced insulin-resistant rats and db/db diabetic mice (205). The gene therapy was able to reduce BP and reverse insulin resistance mediated by an increase in EET. This therapy further led to an improvement in insulin sensitivity through the AMP-activated protein kinases in tissues including liver, muscle, heart, kidney and aorta. Although the results of gene therapy are promising in animal models, further investigation is needed in order to explore whether CYP2J3 gene delivery is feasible and beneficial in humans.

In addition to lifestyle and diet modifications, hypertensive patients with MS should receive pharmacological treatment, according to the recommendations of the ESH (206). The threshold for initiation of antihypertensive treatment is similar for both healthy individuals and subjects with MS: BP-lowering drugs should be given when peripheral BP is persistently *equal to or greater than* 140/90 mmHg. In the presence of diabetes, the threshold for drug intervention is lower, and antihypertensive treatment should be started at BP values *greater than or equal to* 130/85 mmHg. However, the target BP level in both patients with MS and in diabetics should be lower than 130/80 mmHg, in line with current recommendations for individuals with a high cardiovascular risk. Similar goals and an even lower threshold for drug intervention (*below* 130/80 mmHg) should be considered when MS is present in subjects with a very high CV risk, such as in the presence of a history of CV or advanced renal disease.

The ideal BP threshold for antihypertensive drug intervention in MS patients without diabetes or overt CVD is difficult to establish due to the lack of adequately designed randomized trials targeting this subject. Although no available study has tested the long-term benefit of antihypertensive drug initiation at different BP levels in this specific population stratum, it seems reasonable to support early BP-lowering treatment in order to prevent the appearance or progression of target-organ damage (207).

Concerning BP-lowering drug classes, no available trial has investigated the superiority of a specific

antihypertensive drug class as compared to the others in terms of BP and cardiovascular risk reduction in MS patients. However, it is known that each antihypertensive drug class has a different impact on the metabolic profile of hypertensive patients. Given the fact that the development of diabetes or atherogenic dyslipidemia in MS patients confers a considerable increase in cardiovascular risk, certain drug classes should be avoided in MS patients due to their adverse cardiometabolic effect.

Angiotensin-converting enzyme inhibitors (ACEi), angiotensin II-AT1 receptor blockers (ARAI) and calcium channel blockers may induce a reduction of insulin resistance and beneficial changes in lipid profile (208). Therefore, these drug classes are preferable over diuretics and  $\beta$ -blockers in monotherapy if no compelling indications are present for their use. If a combination of drugs is required, low-range doses of diuretics can be introduced. In contrast, a combination of thiazidic diuretics and  $\beta$ -blockers should be avoided due to their potentially adverse cardiometabolic effects (Table 17.2). Despite the current recommendation against the use of  $\beta$ -blockers in MS patients, the potential benefits of vasodilating  $\beta$ -blockers are currently under investigation (209). The majority of studies indicating a reduced protective activity of  $\beta$ -blockers were carried out with atenolol, a  $\beta_1$ -adrenergic selective antagonist. However, the  $\beta$ -blocker family has grown in the past years, and molecules with different selectivity, partial intrinsic sympathetic activity, and vasodilatory capacity have been developed. Vasodilating  $\beta$ -blockers including nebivolol may have a neutral or even favourable cardiometabolic profile as compared to non-vasodilating  $\beta$ -blockers (210,211). Whether or not these molecules improve outcomes in MS patients under antihypertensive treatment needs to be addressed in future trials.

## CONCLUSIONS

MS is a highly prevalent condition characterized by a cluster of clinical and metabolic cardiovascular risk factors including high BP. BP levels are related to MS components: Individuals with elevated BP have a higher risk of the development and progression of MS, and vice versa. In the hypertensive population, the presence of MS confers an increase in cardiovascular risk on top of the risk induced by BP elevation alone. Consequently, the assessment of MS components and BP management based on individual risk is relevant from a clinical point of view in order to reduce morbidity and mortality. The development of hypertension is commonly associated with both obesity and insulin resistance. The main pathophysiological

mechanisms include overactivity of the sympathetic and the renin–angiotensin–aldosterone system, abnormal renal sodium handling, and endothelial dysfunction. The objectives of MS treatment in the hypertensive population are to reduce the elevated cardiovascular and renal risk associated with the individual components of MS and to prevent the development type 2 diabetes. Lifestyle changes, including a healthy diet and regular physical exercise, should be strongly recommended to all MS patients. For pharmacological management, drug classes that favour a reduction of IR and the consequent changes in lipid profile and glucose levels are preferable. Further research is needed in order to establish specific recommendations regarding first-line treatment in individuals with different numbers of MS conditions and different stages of disease severity. In addition to close BP control, a reduction in LDL-cholesterol and glucose levels should be targeted in patients with MS.

## REFERENCES

- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001 May 16; 285(19): 2486–2497.
- Grundy SM, Brewer HB, Cleeman JI et al. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004 January 27; 109(3): 433–438.
- Consensus statements [Internet]. [cited 2017 Dec 4]. Available from: <https://www.idf.org/e-library/consensus-statements/60-idf-consensus-worldwide-definition-of-the-metabolic-syndrome.html>
- Carr DB, Utzschneider KM, Hull RL et al. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. *Diabetes* 2004; 53: 2087–2094.
- Pouliot MC, Després JP, Lemieux S et al. Waist circumference and abdominal sagittal diameter: Best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol* 1994 March 1; 73(7): 460–468.
- Alberti KG, Eckel RH, Grundy SM et al. Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention. In: National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; 120: 1640–1645.
- Slagter SN, van Waateringe RP, van Beek AP et al. Sex, BMI and age differences in metabolic syndrome: The Dutch Lifelines Cohort Study. *Endocr Connect* 2017 May; 6(4): 278–288.
- Brunzell JD, Ayyobi AF. Dyslipidemia in the metabolic syndrome and type 2 diabetes mellitus. *Am J Med* 2003 December 8; 115(Suppl 8A): 24S–28S.
- Reaven GM. The metabolic syndrome: Is this diagnosis necessary? *Am J Clin Nutr* 2006 June; 83(6): 1237–1247.
- Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: Time for a critical appraisal: Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes* 2005; 28: 9.
- Scuteri A, Laurent S, Cucca F et al. Metabolic syndrome across Europe: Different clusters of risk factors. *Eur J Prev Cardiol* 2015 April; 22(4): 486–491.
- Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: Definitions and controversies. *BMC Med [Internet]* 2011 December [cited 2018 Jan 10]; 9(1). Available from: <http://bmc-medicine.biomedcentral.com/articles/10.1186/1741-7015-9-48>
- Mancia G, Fagard R, Narkiewicz K et al. ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013 July; 31(7): 1281–1357.
- Ding EL, Smit LA, Hu FB. The metabolic syndrome as a cluster of risk factors: Is the whole greater than the sum of its parts? Comment on 'The metabolic syndrome, its component risk factors, and progression of coronary atherosclerosis.' *Arch Intern Med* 2010; 170: 484–485.
- Johnson RJ, Kang D-H, Feig D et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension* 2003 June 1; 41(6): 1183–1190.
- Kanellis J, Kang D-H. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. *Semin Nephrol* 2005 January; 25(1): 39–42.
- Dai H, Lu S, Tang X et al. Combined association of serum uric acid and metabolic syndrome with chronic kidney disease in hypertensive patients. *Kidney Blood Press Res* 2016; 41(4): 413–423.
- Choi HK, Ford ES. Prevalence of the metabolic syndrome in individuals with hyperuricemia. *Am J Med* 2007 May; 120(5): 442–447.
- Nejatinamini S, Ataie-Jafari A, Qorbani M et al. Association between serum uric acid level and metabolic syndrome components. *J Diabetes Metab Disord [Internet]* 2015 December [cited 2018 Jan 10]; 14(1). Available from: <http://jdmsonline.biomed-central.com/articles/10.1186/s40200-015-0200-z>
- Ly Q, Meng X-F, He F-F et al. High serum uric acid and increased risk of type 2 diabetes: A systemic review and meta-analysis of prospective cohort studies. Miao X-P (ed). *PLOS ONE* 2013 February 20; 8(2): e56864.
- Kodama S, Saito K, Yachi Y et al. Association between serum uric acid and development of type 2 diabetes. *Diabetes Care* 2009 September 1; 32(9): 1737–1742.
- Oda E. Serum uric acid is an independent predictor of metabolic syndrome in a Japanese health screening population. *Heart Vessels* 2014 July; 29(4): 496–503.
- Sluijs I, Holmes MV, van der Schouw YT et al. A Mendelian randomization study of circulating uric acid and type 2 diabetes. *Diabetes* 2015 August; 64(8): 3028–3036.
- Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: A systematic review and meta-analysis: Risk of incident hypertension associated with hyperuricemia. *Arthritis Care Res* 2011 January; 63(1): 102–110.
- Cicero AFG, Salvi P, D'Addato S et al. Association between serum uric acid, hypertension, vascular stiffness and subclinical atherosclerosis: Data from the Brisighella Heart Study. *J Hypertens* 2014 January; 32(1): 57–64.
- Huang H, Huang B, Li Y et al. Uric acid and risk of heart failure: A systematic review and meta-analysis. *Eur J Heart Fail* 2014 January; 16(1): 15–24.
- Li M, Hou W, Zhang X et al. Hyperuricemia and risk of stroke: A systematic review and meta-analysis of prospective studies. *Atherosclerosis* 2014 February; 232(2): 265–270.
- Agarwal V, Hans N, Messerli FH. Effect of allopurinol on blood pressure: A systematic review and meta-analysis. *J Clin Hypertens Greenwich Conn* 2013 June; 15(6): 435–442.
- Takir M, Kostek O, Ozkok A et al. Lowering uric acid with allopurinol improves insulin resistance and systemic inflammation in asymptomatic hyperuricemia. *J Investig Med* 2015 December; 63(8): 924–929.
- Singh JA, Yu S. Are allopurinol dose and duration of use nephroprotective in the elderly? A Medicare claims study of allopurinol use and incident renal failure. *Ann Rheum Dis* 2017 January; 76(1): 133–139.
- Moore JX, Chaudhary N, Akinyemiju T. Metabolic syndrome prevalence by race/ethnicity and sex in the United States, national health and nutrition examination survey, 1988–2012. *Prev Chronic Dis [Internet]* 2017 March 16 [cited 2017 Dec 29]; 14. Available from: [http://www.cdc.gov/pcd/issues/2017/16\\_0287.htm](http://www.cdc.gov/pcd/issues/2017/16_0287.htm)
- Miller JM, Kaylor MB, Johannsson M et al. Prevalence of metabolic syndrome and individual criterion in US adolescents: 2001–2010 National Health and Nutrition Examination Survey. *Metab Syndr Relat Disord* 2014 December; 12(10): 527–532.
- Falkner B, Cossrow NDFH. Prevalence of metabolic syndrome and obesity-associated hypertension in the racial ethnic minorities of the United States. *Curr Hypertens Rep [Internet]* 2014 July [cited 2018 Jan 10]; 16(7). Available from: <http://link.springer.com/10.1007/s11906-014-0449-5>
- Khan SA, Jackson RT. The prevalence of metabolic syndrome among low-income South Asian Americans. *Public Health Nutr* 2016 February; 19(3): 418–428.
- Gill RM, Khan SA, Jackson RT, Duane M. Prevalence of the metabolic syndrome in central and south American immigrant residents of the Washington, DC, area. *J Nutr Metab* 2017; 2017: 1–6.



36. van Vliet-Ostaptchouk JV, Nuotio M-L, Slagter SN et al. The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: A collaborative analysis of ten large cohort studies. *BMC Endocr Disord [Internet]* 2014 December [cited 2018 Jan 10]; 14(1). Available from: <http://bmcendocrdisord.biomedcentral.com/articles/10.1186/1472-6823-14-9>
37. Day C. Metabolic syndrome, or what you will: Definitions and epidemiology. *Diab Vasc Dis Res* 2007 March; 4(1): 32–38.
38. Bener A, Zirie M, Janahi IM et al. Prevalence of diagnosed and undiagnosed diabetes mellitus and its risk factors in a population-based study of Qatar. *Diabetes Res Clin Pract* 2009 April; 84(1): 99–106.
39. Ford ES, Li C, Zhao G. Prevalence and correlates of metabolic syndrome based on a harmonious definition among adults in the US. *J Diabetes* 2010 September; 2(3): 180–193.
40. Muntner P, He J, Chen J et al. Prevalence of non-traditional cardiovascular disease risk factors among persons with impaired fasting glucose, impaired glucose tolerance, diabetes, and the metabolic syndrome: Analysis of the Third National Health and Nutrition Examination Survey (NHANES III). *Ann Epidemiol* 2004 October; 14(9): 686–695.
41. Kaduka LU, Kombe Y, Kenya E et al. Prevalence of metabolic syndrome among an urban population in Kenya. *Diabetes Care* 2012 April; 35(4): 887–893.
42. Bener A, Zirie M, Musallam M et al. AOAA. Prevalence of metabolic syndrome according to Adult Treatment Panel III and International Diabetes Federation criteria: A population-based study. *Metab Syndr Relat Disord* 2009 June; 7(3): 221–229.
43. Mabry RM, Reeves MM, Eakin EG, Owen N. Gender differences in prevalence of the metabolic syndrome in Gulf Cooperation Council countries: A systematic review. *Diabet Med J Br Diabet Assoc* 2010 May; 27(5): 593–597.
44. Aguilar M, Bhuket T, Torres S et al. Prevalence of the metabolic syndrome in the United States, 2003–2012. *JAMA* 2015 May 19; 313(19): 1973.
45. Isomaa B, Almgren P, Tuomi T et al. morbidity and mortality associated with the metabolic syndrome. *Diabetes* 19 2001; 24: 683–689.
46. Alexander CM LP, Teutsch SM, Haffner SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes* 2003; 52: 1210–1214.
47. Ram CVS, Farmer JA. Metabolic syndrome in South Asians. *J Clin Hypertens (Greenwich)* 2012 August; 14(8): 561–565.
48. Bog-Hansen E, Lindblad U, Gullberg B et al. Metabolic disorders associated with uncontrolled hypertension. Skaraborg Hypertension and Diabetes Project. *Diabetes Obes Metab* 2003 November; 5(6): 379–387.
49. Martell N, Mateo J, Fernandez C et al. Metabolic syndrome and insulin resistance in hypertensives and normotensives with and without family history of hypertension: OP 007. *J Hypertens* 2004 February; 22: S5.
50. Mancía G, Parati G, Borghi C et al. Hypertension prevalence, awareness, control and association with metabolic abnormalities in the San Marino population: The SMOOTH study. *J Hypertens* 2006 May; 24(5): 837–843.
51. Leoncini G, Ratto E, Viazzi F et al. Metabolic syndrome is associated with early signs of organ damage in nondiabetic, hypertensive patients. *J Intern Med* 2005 May; 257(5): 454–460.
52. Mule G, Nardi E, Cottone S et al. Influence of metabolic syndrome on hypertension-related target organ damage. *J Intern Med* 2005 June; 257(6): 503–513.
53. Scholze J, Alegria E, Ferri C et al. Epidemiological and economic burden of metabolic syndrome and its consequences in patients with hypertension in Germany, Spain and Italy: a prevalence-based model. *BMC Public Health* 2010 September 2; 10: 529.
54. Lioudaki E, Vrentzos GE, Zeniodi MH et al. Prevalence of metabolic syndrome according to different definitions in a hypertensive population. *Angiology* 2012; 63: 39–47.
55. Arcucci O, de Simone G, Izzo R et al. Association of suboptimal blood pressure control with body size and metabolic abnormalities. *J Hypertens* 2007 November; 25(11): 2296–2300.
56. De Marco M, de Simone G, Roman MJ et al. Cardiovascular and metabolic predictors of progression of prehypertension into hypertension: The strong heart study. *Hypertension* 2009 November 1; 54(5): 974–980.
57. Xiao J, Hua T, Shen H et al. Associations of metabolic disorder factors with the risk of uncontrolled hypertension: A follow-up cohort in rural China. *Sci Rep [Internet]* 2017 December [cited 2018 Jan 10]; 7(1). Available from: <http://www.nature.com/articles/s41598-017-00789-2>
58. Whelton PK, Carey RM, Aronow WS et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018; 72(3): e33.
59. Mancía G, Bombelli M, Corrao G et al. Metabolic syndrome in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study: Daily life blood pressure, cardiac damage, and prognosis. *Hypertension*. 2007 January; 49(1): 40–47.
60. Bayturan O, Tuzcu EM, Lavoie A et al. The metabolic syndrome, its component risk factors, and progression of coronary atherosclerosis. *Arch Intern Med* 2010 March 8; 170(5): 478–484.
61. Grundy SM. Metabolic syndrome update. *Trends Cardiovasc Med* 2016 May; 26(4): 364–373.
62. Grundy SM. Adipose tissue and metabolic syndrome: Too much, too little or neither. *Eur J Clin Invest* 2015 November; 45(11): 1209–1217.
63. Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. *J Am Coll Cardiol* 2012 February 14; 59(7): 635–643.
64. Kursawe R, Eszlinger M, Narayan D et al. Cellularity and adipogenic profile of the abdominal subcutaneous adipose tissue from obese adolescents: Association with insulin resistance and hepatic steatosis. *Diabetes* 2010 September; 59(9): 2288–2296.
65. McLaughlin T, Lamendola C, Liu A, Abbasi F. Preferential fat deposition in subcutaneous versus visceral depots is associated with insulin sensitivity. *J Clin Endocrinol Metab* 2011 November; 96(11): E1756–E1760.
66. Kumari M, Heeren J, Scheja L. Regulation of immunometabolism in adipose tissue. *Semin Immunopathol* 2017 December 5.
67. Ryckman KK, Borowski KS, Parikh NI, Saftlas AF. Pregnancy complications and the risk of metabolic syndrome for the offspring. *Curr Cardiovasc Risk Rep* 2013 June; 7(3): 217–223.
68. Chassaing B, Koren O, Goodrich JK et al. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature* 2015 March; 519(7541): 92–96.
69. Wilson PWF, Grundy SM. The metabolic syndrome: Practical guide to origins and treatment: Part I. *Circulation* 2003 September 23; 108(12): 1422–1424.
70. Grundy SM, Hansen B, Smith SC et al. Clinical management of metabolic syndrome: Report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. *Arterioscler Thromb Vasc Biol* 2004 February; 24(2): e19–e24.
71. Deedwania P, Barter P, Carmena R et al. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: Analysis of the Treating to New Targets study. *Lancet* 2006; 368: 919–928.
72. Engström G, Hedblad B, Stavenow L et al. Inflammation-sensitive plasma proteins are associated with future weight gain. *Diabetes* 2003 August; 52(8): 2097–2101.
73. Armani A, Berry A, Cirulli F, Caprio M. Molecular mechanisms underlying metabolic syndrome: The expanding role of the adipocyte. *FASEB J* 2017 October; 31(10): 4240–4255.
74. Klötting N, Blüher M. Adipocyte dysfunction, inflammation and metabolic syndrome. *Rev Endocr Metab Disord* 2014 December; 15(4): 277–287.
75. Rajala MW, Scherer PE. Minireview: The adipocyte—at the crossroads of energy homeostasis, inflammation, and atherosclerosis. *Endocrinology* 2003 September; 144(9): 3765–3773.
76. Weisberg SP, McCann D, Desai M et al. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003 December; 112(12): 1796–1808.
77. Lettieri Barbato D, Aquilano K. Feast and famine: Adipose tissue adaptations for healthy aging. *Ageing Res Rev* 2016 July; 28: 85–93.
78. Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. *Science* 2005 January 21; 307(5708): 384–387.
79. Goodpaster BH, He J, Watkins S, Kelley DE. Skeletal muscle lipid content and insulin resistance: Evidence for a paradox in endurance-trained athletes. *J Clin Endocrinol Metab* 2001 December; 86(12): 5755–5761.
80. Tanaka T, Yamamoto J, Iwasaki S et al. Activation of peroxisome proliferator-activated receptor delta induces fatty acid beta-oxidation in skeletal muscle and attenuates metabolic syndrome. *Proc Natl Acad Sci U S A* 2003 December 23; 100(26): 15924–15929.
81. Hardy OT, Czech MP, Corvera S. What causes the insulin resistance underlying obesity? *Curr Opin Endocrinol Diabetes Obes* 2012 April; 19(2): 81–87.
82. Sakkinen PA, Wahl P, Cushman M et al. Clustering of procoagulation, inflammation, and fibrinolysis variables with metabolic

- factors in insulin resistance syndrome. *Am J Epidemiol* 2000 November 15; 152(10): 897–907.
83. Whaley-Connell A, Johnson MS, Sowers JR. Aldosterone: Role in the cardiometabolic syndrome and resistant hypertension. *Prog Cardiovasc Dis* 2010 April; 52(5): 401–409.
  84. Sowers JR, Whaley-Connell A, Epstein M. Narrative review: The emerging clinical implications of the role of aldosterone in the metabolic syndrome and resistant hypertension. *Ann Intern Med* 2009 June 2; 150(11): 776–783.
  85. Ehrhart-Bornstein M, Lamounier-Zepter V, Schraven A et al. Human adipocytes secrete mineralocorticoid-releasing factors. *Proc Natl Acad Sci* 2003 November 25; 100(24): 14211–14216.
  86. Ehrhart-Bornstein M, Arakelyan K, Krug AW et al. Fat cells may be the obesity-hypertension link: Human adipogenic factors stimulate aldosterone secretion from adrenocortical cells. *Endocr Res* 2004 November; 30(4): 865–870.
  87. Huby A-C, Antonova G, Groenendyk J et al. Adipocyte-derived hormone leptin is a direct regulator of aldosterone secretion, which promotes endothelial dysfunction and cardiac fibrosis clinical perspective. *Circulation* 2015 December 1; 132(22): 2134–2145.
  88. de Paula RB, da Silva AA, Hall JE. Aldosterone antagonism attenuates obesity-induced hypertension and glomerular hyperfiltration. *Hypertension* 2004 January; 43(1): 41–47.
  89. de Souza F, Muxfeldt E, Fiszman R, Salles G. Efficacy of spironolactone therapy in patients with true resistant hypertension. *Hypertension* 2010 January; 55(1): 147–152.
  90. Fujita T. Mechanism of salt-sensitive hypertension: Focus on adrenal and sympathetic nervous systems. *J Am Soc Nephrol JASN* 2014 June; 25(6): 1148–1155.
  91. Lamounier-Zepter V, Ehrhart-Bornstein M. Fat tissue metabolism and adrenal steroid secretion. *Curr Hypertens Rep* 2006 April; 8(1): 30–34.
  92. Guo C, Ricchiuti V, Lian BQ et al. Mineralocorticoid receptor blockade reverses obesity-related changes in expression of adiponectin, peroxisome proliferator-activated receptor-gamma, and proinflammatory adipokines. *Circulation* 2008 Apr 29; 117(17): 2253–2261.
  93. Mendizábal Y, Llorens S, Nava E. Hypertension in metabolic syndrome: Vascular pathophysiology. *Int J Hypertens* 2013; 2013: 1–15.
  94. Rahmouni K, Correia MLG, Haynes WG, Mark AL. Obesity-associated hypertension: New insights into mechanisms. *Hypertension* 2005 January; 45(1): 9–14.
  95. Sonnenberg GE, Krakower GR, Kissebah AH. A novel pathway to the manifestations of metabolic syndrome. *Obes Res* 2004 February; 12(2): 180–186.
  96. Hall JE, Brands MW, Henegar JR. Mechanisms of hypertension and kidney disease in obesity. *Ann N Y Acad Sci* 1999 November 18; 892: 91–107.
  97. Kim J, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: Molecular and pathophysiological mechanisms. *Circulation* 2006 April 18; 113(15): 1888–1904.
  98. Sharma V, McNeill JH. The etiology of hypertension in the metabolic syndrome part three: The regulation and dysregulation of blood pressure. *Curr Vasc Pharmacol* 2006 October; 4(4): 321–348.
  99. Nizar JM, Dong W, McClellan RB et al. Na<sup>+</sup>-sensitive elevation in blood pressure is ENaC independent in diet-induced obesity and insulin resistance. *Am J Physiol Ren Physiol* 2016 May; 310(9): F812–F820.
  100. Riaz S, Khan O, Hu X, Ecelbarger CA. Aldosterone infusion with high-NaCl diet increases blood pressure in obese but not lean Zucker rats. *Am J Physiol Renal Physiol* 2006 September; 291(3): F597–F605.
  101. Ecelbarger CM. Metabolic syndrome, hypertension, and the frontier between. *Am J Physiol Ren Physiol* 2016 June; 310(11): F1175–F1177.
  102. Seravalle G, Grassi G. Sympathetic nervous system, hypertension, obesity and metabolic syndrome. *High Blood Press Cardiovasc Prev* 2016 September; 23(3): 175–179.
  103. Troisi RJ, Weiss ST, Parker DR et al. Relation of obesity and diet to sympathetic nervous system activity. *Hypertension* 1991 May; 17(5): 669–677.
  104. Vaz M, Jennings G, Turner A, Cox H, Lambert G, Esler M. Regional sympathetic nervous activity and oxygen consumption in obese normotensive human subjects. *Circulation* 1997 November 18; 96(10): 3423–3429.
  105. Grassi G, Dell’Oro R, Facchini A et al. Effect of central and peripheral body fat distribution on sympathetic and baroreflex function in obese normotensives. *J Hypertens* 2004 December; 22(12): 2363–2369.
  106. Grassi G, Colombo M, Seravalle G et al. Dissociation between muscle and skin sympathetic nerve activity in essential hypertension, obesity, and congestive heart failure. *Hypertension* 1998 January; 31(1): 64–67.
  107. Young JB, Macdonald IA. Sympathoadrenal activity in human obesity: Heterogeneity of findings since 1980. *Int J Obes Relat Metab Disord J Int Assoc Study Obes* 1992 December; 16(12): 959–967.
  108. Adams MA, Thompson KE, Banting JD, Madigan MA, Friberg P. Evidence *in vivo* for induction of cardiovascular growth processes by vasoconstrictor systems. *Blood Press Suppl* 1995; 2: 61–67.
  109. Cabandugama PK, Gardner MJ, Sowers JR. The renin angiotensin aldosterone system in obesity and hypertension: Roles in the cardiorenal metabolic syndrome. *Med Clin North Am* 2017 January; 101(1): 129–137.
  110. Kamide K. Role of renin-angiotensin-aldosterone system in metabolic syndrome and obesity-related hypertension. *Curr Hypertens Rev* 2014 August 12.
  111. Boustany CM, Bharadwaj K, Daugherty A et al. Activation of the systemic and adipose renin-angiotensin system in rats with diet-induced obesity and hypertension. *Am J Physiol Regul Integr Comp Physiol* 2004 October; 287(4): R943–R949.
  112. Li X, Meng X, Timofeeva M et al. Serum uric acid levels and multiple health outcomes: Umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies. *BMJ* 2017 June 7; 357: j2376.
  113. Watanabe S, Kang D-H, Feng L et al. Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. *Hypertension* 2002 September; 40(3): 355–360.
  114. Cebollada J, Gimeno JA. Ácido úrico como factor de riesgo cardiovascular. *Hipertens Riesgo Vasc* 2012 April; 29(2): 36–43.
  115. Kanbay M, Segal M, Afsar B et al. The role of uric acid in the pathogenesis of human cardiovascular disease. *Heart* 2013 June 1; 99(11): 759–766.
  116. Sharaf El Din UAA, Salem MM, Abdulazim DO. Uric acid in the pathogenesis of metabolic, renal, and cardiovascular diseases: A review. *J Adv Res* 2017 September; 8(5): 537–548.
  117. Zhang J, Zhang Y, Deng W, Chen B. Elevated serum uric acid is associated with angiotensinogen in obese patients with untreated hypertension. *J Clin Hypertens* 2014 August; 16(8): 569–574.
  118. Soletsky B, Feig DI. Uric acid reduction rectifies prehypertension in obese adolescents. *Hypertension* 2012 November; 60(5): 1148–1156.
  119. Massiera F, Bloch-Faure M, Ceiler D et al. Adipose angiotensinogen is involved in adipose tissue growth and blood pressure regulation. *FASEB J* 2001 December; 15(14): 2727–2729.
  120. Manolis AJ, Poulimenos LE, Kallistratos MS et al. Sympathetic overactivity in hypertension and cardiovascular disease. *Curr Vasc Pharmacol* 2014 January; 12(1): 4–15.
  121. Goodfriend TL, Calhoun DA. Resistant hypertension, obesity, sleep apnea, and aldosterone: Theory and therapy. *Hypertension* 2004 March; 43(3): 518–524.
  122. Buglioni A, Cannone V, Cataliotti A et al. Circulating aldosterone and natriuretic peptides in the general community: Relationship to cardiorenal and metabolic disease. *Hypertension* 2015 January; 65(1): 45–53.
  123. Goodfriend TL, Ball DL, Egan BM et al. Epoxy-keto derivative of linoleic acid stimulates aldosterone secretion. *Hypertension* 2004 February; 43(2): 358–363.
  124. Hall JE, do Carmo JM, da Silva AA et al. Obesity-induced hypertension: Interaction of neurohumoral and renal mechanisms. *Circ Res* 2015 March 13; 116(6): 991–1006.
  125. Redon J, Lurbe E. *Ambulatory blood pressure: implications for renal dysfunction. In: Calcium Antagonists in Clinical Medicine.* Hanley & Belfus, Philadelphia, PA; 2002: 665–680.
  126. Rojas E, Rodríguez-Molina D, Bolli P et al. The role of adiponectin in endothelial dysfunction and hypertension. *Curr Hypertens Rep* 2014 August; 16(8): 463.
  127. Zhang X, Zhang R, Raab S et al. Rhesus macaques develop metabolic syndrome with reversible vascular dysfunction responsive to pioglitazone. *Circulation* 2011 July 5; 124(1): 77–86.
  128. Montagnani M, Golovchenko I, Kim I et al. Inhibition of phosphatidylinositol 3-kinase enhances mitogenic actions of insulin in endothelial cells. *J Biol Chem* 2002 January 18; 277(3): 1794–1799.
  129. Yang Z, Kaye DM. Endothelial dysfunction and impaired L-arginine transport in hypertension and genetically predisposed normotensive subjects. *Trends Cardiovasc Med* 2006 May; 16(4): 118–124.
  130. Nystrom FH, Quon MJ. Insulin signalling: Metabolic pathways and mechanisms for specificity. *Cell Signal* 1999 August; 11(8): 563–574.



131. Chen H, Montagnani M, Funahashi T et al. Adiponectin stimulates production of nitric oxide in vascular endothelial cells. *J Biol Chem* 2003 November 7; 278(45): 45021–45026.
132. Ohashi K, Kihara S, Ouchi N et al. Adiponectin replenishment ameliorates obesity-related hypertension. *Hypertension* 2006 June; 47(6): 1108–1116.
133. Tan KCB, Xu A, Chow WS et al. Hypoadiponectinemia is associated with impaired endothelium-dependent vasodilation. *J Clin Endocrinol Metab* 2004 February; 89(2): 765–769.
134. Arunkumar Achari, Sushil Jain. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. *Int J Mol Sci* 2017 June 21; 18(6): 1321.
135. Chung C-M, Lin T-H, Chen J-W et al. A genome-wide association study reveals a quantitative trait locus of adiponectin on CDH13 that predicts cardiometabolic outcomes. *Diabetes* 2011 September; 60(9): 2417–2423.
136. Fava C, Danese E, Montagnana M et al. A variant upstream of the CDH13 adiponectin receptor gene and metabolic syndrome in Swedes. *Am J Cardiol* 2011 November 15; 108(10): 1432–1437.
137. Li P, Jiang R, Li L et al. Correlation of serum adiponectin and adiponectin gene polymorphism with metabolic syndrome in Chinese adolescents. *Eur J Clin Nutr* 2015 January; 69(1): 62–67.
138. Giannattasio C. Acute effect of high-fat meal on endothelial function in moderately dyslipidemic subjects. *Arterioscler Thromb Vasc Biol* 2004 November 29; 25(2): 406–410.
139. Tabara Y, Takahashi Y, Kawaguchi T et al. Association of serum-free fatty acid level with reduced reflection pressure wave magnitude and central blood pressure novelty and significance: The Nagahama Study. *Hypertension* 2014 December; 64(6): 1212–1218.
140. Guo S-X, Yan Y-Z, Mu L-T et al. Association of serum free fatty acids with hypertension and insulin resistance among rural Uyghur adults in far Western China. *Int J Environ Res Public Health* 2015 June 9; 12(6): 6582–6590.
141. Scuteri A, Najjar SS, Muller DC et al. Metabolic syndrome amplifies the age-associated increases in vascular thickness and stiffness. *J Am Coll Cardiol* 2004 April 21; 43(8): 1388–1395.
142. Mulè G. Metabolic syndrome in hypertensive patients: An unholy alliance. *World J Cardiol* 2014; 6(9): 890.
143. Mulè G, Cottone S, Nardi E et al. Metabolic syndrome in subjects with essential hypertension: Relationships with subclinical cardiovascular and renal damage. *Minerva Cardioangi* 2006 April; 54(2): 173–194.
144. Mulè G, Cerasola G. The metabolic syndrome and its relationship to hypertensive target organ damage. *J Clin Hypertens (Greenwich)* 2006 March; 8(3): 195–201.
145. Redon J, Cifkova R, Laurent S et al. The metabolic syndrome in hypertension: European society of hypertension position statement. *J Hypertens* 2008 October; 26(10): 1891–1900.
146. Schillaci G, Pirro M, Pucci G et al. Different impact of the metabolic syndrome on left ventricular structure and function in hypertensive men and women. *Hypertension* 2006 May; 47(5): 881–886.
147. Schillaci G, Pirro M, Vaudo G et al. Prognostic value of the metabolic syndrome in essential hypertension. *J Am Coll Cardiol* 2004 May; 43(10): 1817–1822.
148. Cuspidi C, Meani S, Fusi V et al. Metabolic syndrome and target organ damage in untreated essential hypertensives. *J Hypertens* 2004 October; 22(10): 1991–1998.
149. Pannier B, Thomas F, Bean K et al. The metabolic syndrome: Similar deleterious impact on all-cause mortality in hypertensive and normotensive subjects. *J Hypertens* 2008 June; 26(6): 1223–1228.
150. Pierdomenico SD, Lapenna D, Di Tommaso R et al. Prognostic relevance of metabolic syndrome in hypertensive patients at low-to-medium risk. *Am J Hypertens* 2007 December; 20(12): 1291–1296.
151. Andreadis EA, Tsourous GI, Tzavara CK et al. Metabolic syndrome and incident cardiovascular morbidity and mortality in a Mediterranean hypertensive population. *Am J Hypertens* 2007 May; 20(5): 558–564.
152. Vlek ALM, van der Graaf Y, Spiering W et al. Effect of metabolic syndrome or type II diabetes mellitus on the occurrence of recurrent vascular events in hypertensive patients. *J Hum Hypertens* 2008 May; 22(5): 358–365.
153. Gupta AK, Dahlof B, Sever PS, Poulter NR, for the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) Investigators. Metabolic syndrome, independent of its components, is a risk factor for stroke and death but not for coronary heart disease among hypertensive patients in the ASCOT-BPLA. *Diabetes Care* 2010 July 1; 33(7): 1647–1651.
154. Al-Daydamony MM, El-Tahlawi M. What is the effect of metabolic syndrome without hypertension on left ventricular hypertrophy? *Echocardiography* 2016 September; 33(9): 1284–1289.
155. de Simone G. State of the heart in the metabolic syndrome. *Nutr Metab Cardiovasc Dis* 2005; 15(4): 239–241.
156. Cuspidi C, Meani S, Fusi V et al. Prevalence and correlates of left atrial enlargement in essential hypertension: Role of ventricular geometry and the metabolic syndrome: The Evaluation of Target Organ Damage in Hypertension study. *J Hypertens* 2005 April; 23(4): 875–882.
157. Burchfiel CM, Skelton TN, Andrew ME et al. Metabolic syndrome and echocardiographic left ventricular mass in blacks: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 2005 August 9; 112(6): 819–827.
158. Halldin M, Fahlstadius P, de Faire U et al. The metabolic syndrome and left ventricular hypertrophy – the influence of gender and physical activity. *Blood Press* 2012 June; 21(3): 153–160.
159. Cuspidi C, Sala C, Lonati L et al. Metabolic syndrome, left ventricular hypertrophy and carotid atherosclerosis in hypertension: A gender-based study. *Blood Press* 2013 June; 22(3): 138–143.
160. Cuspidi C, Meani S, Valerio C et al. Ambulatory blood pressure, target organ damage and left atrial size in never-treated essential hypertensive individuals. *J Hypertens* 2005 August; 23(8): 1589–1595.
161. Su G, Cao H, Xu S et al. Left atrial enlargement in the early stage of hypertensive heart disease: A common but ignored condition. *J Clin Hypertens (Greenwich)* 2014 March; 16(3): 192–197.
162. Watanabe H, Tanabe N, Watanabe T et al. Metabolic syndrome and risk of development of atrial fibrillation: The Niigata preventive medicine study. *Circulation* 2008 March 11; 117(10): 1255–1260.
163. Tanner RM, Baber U, Carson AP et al. Association of the metabolic syndrome with atrial fibrillation among United States adults (from the REasons for Geographic and Racial Differences in Stroke [REGARDS] Study). *Am J Cardiol* 2011 July 15; 108(2): 227–232.
164. Nyström PK, Carlsson AC, Leander K et al. Obesity, metabolic syndrome and risk of atrial fibrillation: A Swedish, prospective cohort study. Maeda N (ed). *PLOS ONE* 2015 May 15; 10(5): e0127111.
165. Palaniappan L, Carnethon M, Fortmann SP. Association between microalbuminuria and the metabolic syndrome: NHANES III. *Am J Hypertens* 2003 November; 16(11 Pt 1): 952–958.
166. Li X-H, Lin H-Y, Wang S-H et al. Association of microalbuminuria with metabolic syndrome among aged population. *Biomed Res Int* 2016; 2016: 1–7.
167. Lee Y-Y, Yang C-K, Weng Y-M et al. All components of metabolic syndrome are associated with microalbuminuria in a Chinese population. Li Y (ed). *PLOS ONE* 2016 June 21; 11(6): e0157303.
168. Chen J, Muntner P, Hamm LL et al. The metabolic syndrome and chronic kidney disease in U.S. adults. *Ann Intern Med* 2004 February 3; 140(3): 167–174.
169. Kurella M. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *J Am Soc Nephrol* 2005 April 20; 16(7): 2134–2140.
170. Gomez P, Ruilope LM, Barrios V et al. Prevalence of renal insufficiency in individuals with hypertension and obesity/overweight: The FATH study. *J Am Soc Nephrol* 2006 December 1; 17(12 suppl\_3): S194–S200.
171. Tanaka H, Shiohira Y, Uezu Y et al. Metabolic syndrome and chronic kidney disease in Okinawa, Japan. *Kidney Int* 2006 January; 69(2): 369–374.
172. Thomas G, Sehgal AR, Kashyap SR et al. Metabolic syndrome and kidney disease: A systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2011 October 1; 6(10): 2364–2373.
173. Nashar K, Egan B. Relationship between chronic kidney disease and metabolic syndrome: Current perspectives. *Diabetes Metab Syndr Obes Targets Ther* 2014 September; 7: 421.
174. Kawamoto R, Tomita H, Oka Y et al. Metabolic syndrome amplifies the LDL-cholesterol associated increases in carotid atherosclerosis. *Intern Med Tokyo Jpn* 2005 December; 44(12): 1232–1238.
175. Cuspidi C, Sala C, Provenzano F et al. Metabolic syndrome and subclinical carotid damage: A meta-analysis from population-based studies. *J Hypertens* 2018 January; 36(1): 23–30.
176. Scuteri A, Franco OH, Majidi A et al. The relationship between the metabolic syndrome and arterial wall thickness: A mosaic still to be interpreted. *Atherosclerosis* 2016 December; 255: 11–16.
177. Safar ME, et al. Metabolic syndrome and age-related progression of aortic stiffness. *J Am Coll Cardiol* 2006 January; 47(1): 72–75.

178. Scuteri A, Cunha PG, Agabiti Rosei E et al. Arterial stiffness and influences of the metabolic syndrome: A cross-countries study. *Atherosclerosis* 2014 April; 233(2): 654–660.
179. Nam S-H, Kang S-G, Lee Y-A et al. Association of metabolic syndrome with the cardioankle vascular index in asymptomatic Korean population. *J Diabetes Res* 2015; 2015: 1–7.
180. Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK et al. Metabolic syndrome and risk of incident cardiovascular events and death: A systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol* 2007 January 30; 49(4): 403–414.
181. Roger VL, Go AS, Lloyd-Jones DM et al. Heart disease and stroke statistics--2011 update: A report from the American Heart Association. *Circulation* 2011 February 1; 123(4): e18–209.
182. Mottillo S, Filion KB, Genest J et al. The metabolic syndrome and cardiovascular risk. *J Am Coll Cardiol* 2010 September; 56(14): 1113–1132.
183. Franco OH, Massaro JM, Civil J et al. Trajectories of entering the metabolic syndrome: The Framingham Heart Study. *Circulation* 2009 November 17; 120(20): 1943–1950.
184. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Low triglycerides-high high-density lipoprotein cholesterol and risk of ischemic heart disease. *Arch Intern Med* 2001 February 12; 161(3): 361–366.
185. Onat A, Hergenç G, Sari I et al. Dyslipidemic hypertension: Distinctive features and cardiovascular risk in a prospective population-based study. *Am J Hypertens* 2005 March; 18(3): 409–416.
186. Dekker JM, Girman C, Rhodes T et al. Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. *Circulation* 2005 August 2; 112(5): 666–673.
187. López-Suárez A, Bascañana-Quirell A, Beltrán-Robles M et al. Metabolic syndrome does not improve the prediction of 5-year cardiovascular disease and total mortality over standard risk markers. Prospective population based study. *Medicine (Baltimore)* 2014 December; 93(27): e212.
188. Bassi N, Karagodin I, Wang S et al. Lifestyle modification for metabolic syndrome: A systematic review. *Am J Med* 2014 December; 127(12): 1242.e1–10.
189. Lee D-C, Sui X, Church TS et al. Changes in fitness and fatness on the development of cardiovascular disease risk factors hypertension, metabolic syndrome, and hypercholesterolemia. *J Am Coll Cardiol* 2012 February 14; 59(7): 665–672.
190. Jae SY, Babu AS, Yoon ES et al. Impact of cardiorespiratory fitness and risk of systemic hypertension in nonobese versus obese men who are metabolically healthy or unhealthy. *Am J Cardiol* 2017 September 1; 120(5): 765–768.
191. Grundy SM, Barlow CE, Farrell SW et al. Cardiorespiratory fitness and metabolic risk. *Am J Cardiol* 2012 April 1; 109(7): 988–993.
192. Bakker EA, Lee D, Sui X et al. Association of resistance exercise, independent of and combined with aerobic exercise, with the incidence of metabolic syndrome. *Mayo Clin Proc* 2017 August; 92(8): 1214–1222.
193. Lackland DT, Voeks JH. Metabolic syndrome and hypertension: Regular exercise as part of lifestyle management. *Curr Hypertens Rep* 2014 November; 16(11): 492.
194. Golbidi S, Laher I. Exercise induced adipokine changes and the metabolic syndrome. *J Diabetes Res* 2014; 2014: 1–16.
195. Masquio DCL, de Piano A, Campos RMS et al. The role of multicomponent therapy in the metabolic syndrome, inflammation and cardiovascular risk in obese adolescents. *Br J Nutr* 2015 June 28; 113(12): 1920–1930.
196. Egan BM, Laken MA, Donovan JL, Woolson RF. Does dark chocolate have a role in the prevention and management of hypertension? commentary on the evidence. *Hypertension* 2010 June; 55(6): 1289–1295.
197. Taubert D, Roesen R, Lehmann C et al. Effects of low habitual cocoa intake on blood pressure and bioactive nitric oxide: A randomized controlled trial. *JAMA* 2007 July 4; 298(1): 49–60.
198. Jia L, Liu X, Bai YY et al. Short-term effect of cocoa product consumption on lipid profile: A meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2010 July; 92(1): 218–225.
199. Ried K, Sullivan T, Fakler P et al. Does chocolate reduce blood pressure? A meta-analysis. *BMC Med* 2010 June 28; 8: 39.
200. Ried K, Fakler P, Stocks NP. Effect of cocoa on blood pressure. Cochrane Hypertension Group (ed). *Cochrane Database Syst Rev [Internet]* 2017 April 25 [cited 2018 Jan 10]; Available from: <http://doi.wiley.com/10.1002/14651858.CD008893.pub3>
201. Ludovici V, Barthelme J, Nägele MP et al. Cocoa, blood pressure, and vascular function. *Front Nutr [Internet]* 2017 August 2 [cited 2018 Jan 10]; 4. Available from: <http://journal.frontiersin.org/article/10.3389/fnut.2017.00036/full>
202. Strat KM, Rowley TJ, Smithson AT et al. Mechanisms by which cocoa flavanols improve metabolic syndrome and related disorders. *J Nutr Biochem* 2016 September; 35: 1–21.
203. Salas-Salvado J, Guasch-Ferre M, Bullo M, Sabate J. Nuts in the prevention and treatment of metabolic syndrome. *Am J Clin Nutr* 2014 July 1; 100(Supplement\_1): 399S–407S.
204. Chen J, Gu D, Huang J et al. Metabolic syndrome and salt sensitivity of blood pressure in non-diabetic people in China: A dietary intervention study. *Lancet* 2009 March 7; 373(9666): 829–835.
205. Xu X, Zhao CX, Wang L et al. *Diabetes* 2010 April 1; 59(4): 997–1005.
206. Redon J, Cifkova R, Laurent S et al. Mechanisms of hypertension in the cardiometabolic syndrome. *J Hypertens* 2009 March; 27(3): 441–451.
207. Bittner V, Bertolet M, Barraza Felix R et al. Comprehensive cardiovascular risk factor control improves survival. *J Am Coll Cardiol* 2015 August; 66(7): 765–773.
208. Nesbitt SD. Lessons in hypertension from new clinical trials. *Postgrad Med* 2009 November; 121(6): 34–43.
209. Ripley TL, Saseen JJ.  $\beta$ -Blockers: A review of their pharmacological and physiological diversity in hypertension. *Ann Pharmacother* 2014 June; 48(6): 723–733.
210. Taylor AA, Bakris GL. The role of vasodilating beta-blockers in patients with hypertension and the cardiometabolic syndrome. *Am J Med* 2010 July; 123(7 Suppl 1): S21–S26.
211. Fongemie J, Felix-Getzik E. A review of nebivolol pharmacology and clinical evidence. *Drugs* 2015 August; 75(12): 1349–1371.



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# PSYCHOSOCIAL RISK FACTORS, AIRBORNE POLLUTION, HYPERTENSION AND CARDIOVASCULAR DISEASES

# 18

*Philippe van de Borne*

## INTRODUCTION

The various effects of psychological and social factors on cardiovascular events have been reported in numerous publications, where low socioeconomic status, social isolation as well as low social support, stress at work or at home or both, increased the risk of cardiovascular disease. In addition, depressive mood and to a larger extent, clinical depression, anxiety and personality traits such as hostility, anger, and the conjunction of negative affectivity and social inhibition increased the odds ratio of cardiovascular disease.

## LOW SOCIOECONOMIC STATUS

Men and women with low socioeconomic status have an increased all-cause as well as cardiovascular disease and mortality risk (1–5). This derives from several prospective studies (1–5). The mechanisms linking low economic status to mortality are multiple, ranging from less healthy behaviours (diet, physical activity, alcohol consumption etc.) (2) to financial barriers to healthcare (5). Definition of low socioeconomic status encompasses living in a poor residential region, having a low-status employment and a low wage, often as a result of a low educational level (1–5).

## SOCIAL ASPECTS

Social isolation, either due to a lack of relationships with other members of the community or as a result of the absence of social support toward the isolated person, is a risk factor for premature cardiovascular mortality (6,7). This is also observed after the relapse of a cardiovascular event, resulting in a poorer prognosis and recovery (6,7).

## STRESS IN DAILY LIFE

Recurrent expositions to stressful conditions at work may lead to an enhanced cardiovascular risk, although the

evidence is not very strong and is mainly restricted to men, while the accumulated evidence is scarce in women (8,9). Conversely, a stressful family life with constant conflicts empowers the risk of coronary heart disease, and does so mostly in women (10,11).

## DEPRESSIVE MOOD

Subjects who present depressive symptoms or, worse, who demonstrate clinical depression, are also at higher risk of coronary heart disease, and this translates into an impaired recovery and a poorer prognosis after the event (12–14). This is improved by social support (6,7). The opposite condition further enhances the negative effects of depression on cardiovascular prognosis (14–17). Remarkably, the sizable effects of these conditions suggest that depression and social isolation are often associated with a cluster of other cardiovascular risk factors, which may account for the link between depression and cardiovascular prognosis. This assumption is supported by the evidence that the pharmacological therapy of depression does not improve cardiovascular prognosis (14–18). The patient who hosts a large array of negative emotions for prolonged periods of time, which are not shared with others as a result of a reluctance to engage in social contacts, resulting in social inhibition, discloses a type D personality. This condition is related to a poorer prognosis in patients with established cardiovascular disease, even after multiple adjustments (19,20). In mitigation, however, it is difficult to normalize for confounding factors such as depression (12–18), which encompasses also the negative emotions of the type D personality (19,20). Moreover, this condition is often associated with social isolation (6,7), a less healthy lifestyle, and perhaps a poorer socioeconomic status (1–5).

## ANXIETY

Whether anxiety has an adverse effect on cardiovascular disease is not entirely clear. While panic attacks may have raised cardiovascular events to some extent (21,29,30), other forms of anxiety such as phobic anxiety did not

(22–24). Conversely, total mortality was even lower in patients with documented cardiovascular disease and anxiety unless systolic ventricular function was impaired. These bidirectional effects of anxiety on health in patients at risk suggest that other factors may be involved. An alternative interpretation could be that in some circumstances, anxiety may improve adherence to therapy and thereby prognosis, while in other circumstances, anxiety accompanies a severe disabling disease such as heart failure, where the prognosis is poor. Interestingly, after correction for several confounding factors, anxiety appeared nevertheless an independent risk factor for ischaemic heart disease and subsequent poor outcome when studies were pooled into meta-analyses (25,26).

### PERSONALITY TRAITS

Patients, colleagues or family members who express extensive mistrust and demonstrate repeatedly aggressive behaviours where anger and rage tend to preclude normal social relationships often present the well-known personality trait called hostility (27,28). This has been shown to increase the incidence of new and recurrent cardiovascular events (27). Suppressing anger expression predicts excess risk in patients with cardiovascular disease (28), while the reverse condition could contribute to increasing the daily life stress of colleagues and family members (8–11).

### RECENT INSIGHTS

Several studies have further pooled individual and published data from cohorts into large databases in order to better understand the association between stress and cardiovascular disease. While marriage remains accompanied by a lower cardiovascular disease rate, and after a cardiovascular event, marital status is associated with an improved prognosis (29). The reverse occurs in the presence of depression or lack social support (29). In a general population at work, job strain should be removed from 550 employees for 5 years to prevent one myocardial infarction (30). In comparison, antihypertensive therapy in intermediate cardiovascular risk individuals is 6–7 times more efficacious to prevent one major cardiovascular event (31). Recent evidence indicates that in the general population, work and private-life stress increases the risk of incident coronary heart disease and stroke by 1.1- to 1.6-fold (32). Accordingly, a Cochrane systematic review and meta-analysis of psychological interventions for coronary heart disease reported a reduction in cardiovascular mortality (relative risk 0.79%, 95% confidence interval [CI] 0.63–0.98) and favourable effects on depressive symptoms, anxiety and stress (32).

### SUMMARY

Low socioeconomic status, lack of social support, stress at work and in family life, depression, anxiety, hostility, and the type D personality not only contribute to the risk of developing cardiovascular disease but also worsen its clinical course. These risk factors are often associated with other risk factors such as unhealthy diet, lack of physical

activity, alcohol consumption and financial barriers to healthcare. Psychological interventions for coronary heart disease modestly reduce cardiovascular mortality and improve mental health in meta-analysis.

### OTHER CARDIOVASCULAR RISK FACTORS: AIRBORNE POLLUTION AND HYPERTENSION

Air pollution is a ubiquitous and highly heterogeneous mixture of particulate matter (PM), various gaseous compounds and molecules in vapor phase (33). The gaseous part of polluted air encompasses nitrogen oxides, sulphur oxides, and ozone, while PM includes different elements such as nitrates, sulphates, transition metals and organic and elemental carbon. Fine PM ( $<2.5 \mu\text{m}$  in diameter;  $\text{PM}_{2.5}$ ) is linked to cardiovascular morbidity and mortality excess (33). Epidemiological studies have shown that short-term rises in  $\text{PM}_{2.5}$  are accompanied within a few days by additional myocardial infarcts, heart failure exacerbations, cardiac arrhythmias and strokes.

### POSSIBLE MECHANISMS OF DISEASE

Several mechanisms may explain these observations: (i) an acute autonomic nervous system imbalance, due to  $\text{PM}_{2.5}$  accumulation within the pulmonary tree and activation of nerve endings and receptors (34), and (ii) an inflammatory response to air pollution in the lungs, with extended effects outside the pulmonary vasculature (35). Subsequent cytokine release and immune cell activation then result in further oxidative stress and endothelial dysfunction. Tumour necrosis factor, interleukin 6, endothelin and activated leukocytes can also induce systemic upregulation of reactive oxygen species pathways through nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and promote endothelial nitric oxide synthase (eNOS) uncoupling.  $\text{PM}_{2.5}$  exposure reduces tetrahydropterin level in various organs, and these effects may persist for weeks after the inhalation (35). Enhanced vascular responsiveness to a variety of vasoactive substances further reveals that airborne pollution shifts vasomotor tone towards vasoconstriction (35). Endothelium-dependent vasodilation impairment is related to PM exposition not only in higher-risk individuals (e.g. those with diabetes) but also in healthy adults (36,37). Moreover, among elderly subjects, a reduction in 48-hour  $\text{PM}_{2.5}$  levels due to filtering of air in subjects' homes resulted in improved microvascular function (38). These abnormalities are more likely to be due to a decreased nitric oxide bioavailability as a consequence of systemic inflammation or oxidative stress. This may explain why  $\text{PM}_{10}$  air pollution levels are associated with heightened amplitude of the reflection wave leading to significant alterations in central pulse pressure (39). Last, inhalation of some metallic components, as well as very small particles, may impair vasomotor regulation after reaching the circulation directly. As such, passive smoking not only increases plasma nicotine levels and wave reflection when compared to nontobacco smoke (40) but also results in higher blood pressure levels in children of smoking parents (41). In the latter study,



parental smoking independently affected systolic blood pressure even after correction for other risk factors such as body mass index, parental hypertension or birth weight. Interestingly, the quantitative relationship was established for maternal, but not parental, cigarette consumption. This is likely because mothers are more likely to smoke predominantly at home, whereas fathers may consume their cigarettes at work or outside of the home, and thus in the absence of the children.

## BLOOD PRESSURE AND AIRBORNE POLLUTION

Does acute exposure to airborne pollution increase blood pressure, and are hypertensive patients at risk or protected against these effects?

## EXPERIMENTAL STUDIES

Controlled animal studies have been performed under different conditions, using different recording systems (mainly tail-cuff and radio telemetry) and not surprisingly, have reported variable results where blood pressure remained unchanged, decreased (when very large amounts of PM are administered intrabronchially or intravenously) or increased. In controlled human studies (middle-aged or elderly healthy adults and patients with coronary artery disease), blood pressure remained either unchanged or increased in most of the publications (42). However, using a controlled experimental design in healthy humans specifically dedicated to study the impact of PM exposure on blood pressure, it has been shown that exposure to PM increases diastolic blood pressure rapidly (42,43).

## EVIDENCE FROM EPIDEMIOLOGICAL STUDIES

There is an association between daily levels of nitrogen dioxide (NO<sub>2</sub>), sulphur dioxide (SO<sub>2</sub>), and PM<sub>10</sub> and emergency department visits for hypertension in Canada, with a 3-day lag (44). This association is also observed between PM<sub>10</sub> and PM<sub>2.5</sub> with a 6-day lag. Similar associations, but for much larger PM levels, have been reported in China and Brazil (45,46). The true effects of air pollution on blood pressure could even be larger than the 6% increased risk for emergency visit for hypertension (44), because elevations in blood pressure will remain unnoticed in most patients. A large study on adults older than 30 years of age participating in the National Health Interview Survey demonstrated a significant association between self-reported hypertension and annual PM<sub>2.5</sub> exposure estimation using US Environmental Protection Agency (EPA) monitoring data (47). An increment of 10 µg/m<sup>3</sup> PM<sub>2.5</sub> was associated with an adjusted odds ratio of 1.05 (CI 1.00–1.10) for the presence of hypertension.

A higher left ventricular mass index as measured by cardiac magnetic resonance imaging was demonstrated to be associated with residential proximity to major roadways in a report from the Multi-Ethnic Study of Atherosclerosis (48). The degree of increase was analogous to a 5.6-mmHg increase in systolic blood pressure among the study participants. This suggests that traffic-related exposures may have increased left ventricular mass by chronically elevating

systemic arterial blood pressure, a common cause of left ventricular hypertrophy. Elevated ambient PM<sub>2.5</sub> levels are associated, within 3–5 days, with systolic and diastolic blood pressure elevations (49), unless heart rate was lower than 70 bpm in these cardiac rehabilitation patients, suggesting that cardiovascular medication may protect against the hypertensive effects of air pollution. A study in South Korea (50) and a study in six US cities (51) also observed these associations. In the latter study, adjusted blood pressure rose within 1–2 days by 3 mmHg, and this association was stronger in patients with hypertension as well as under other conditions such as warm weather and traffic proximity. A study in Detroit (52) reported a 3-mmHg increase in systolic blood pressure per 10 µg/m<sup>3</sup> rise in PM<sub>2.5</sub> with a lag of 2 days. However, similar rises in PM<sub>2.5</sub> did not result in comparable blood pressure effects in the different districts of Detroit, and this was attributed to differences in PM composition. The composition, concentration and dimension of the particles give a specific toxicity profile to the particles and may explain the seasonal variation in the strength of the association between PM exposure and blood pressure (50). In the warm weather season, the effect of PM<sub>10</sub> on blood pressure increase is more consistent than in the cold weather season. Finally, changes in systolic blood pressure were not significant in patients taking antihypertensive medications (+0.7 mmHg), as compared to those who were untreated (+6 mmHg).

On the other hand, a large meta-analysis suggested that air pollution is an important trigger for myocardial infarction, even more than a classic cardiovascular risk factor (53). Trigger studies in this case typically assessed risk exposure in the period ranging from a few minutes to 24 hours before the onset of myocardial infarction. Air pollution exposure induced a small individual odds ratio for cardiovascular events but had a large and significant impact on the whole population. These effects may be more pronounced in patients with markedly elevated cardiovascular risk factors.

## ACUTE VERSUS CHRONIC EFFECTS OF AIRBORNE POLLUTION ON HYPERTENSION AND CARDIOVASCULAR DISEASE

Pollution peaks have an acute effect on blood pressure. As such, airborne pollution appears more as a triggering factor of cardiovascular events than a persistent cardiovascular risk factor by itself.

Whether chronic exposure to pollution induces sustained increases in blood pressure is not yet well established. There is, however, mounting evidence suggesting that this may be the case. For example, it has been shown that people living close to major highways present an increased left ventricular mass (48). Moreover, self-reported hypertension was positively linked to estimated chronic PM exposure in a survey of more than 130,000 adults (47). A population-based prospective cohort in Germany of 4291 participants, where baseline data had been gathered between 2000 and 2003, showed that that an interquartile increase in PM<sub>2.5</sub> of 2.4 µg/m<sup>3</sup> was associated with an increase in systolic blood pressure of 1.4 mmHg and diastolic blood pressure of 0.9 mmHg (54). This relationship was independent of long-term exposure to road traffic noise and robust to the inclusion of many

potential confounders. Thus, in this study, long-term exposure to PM was clearly associated with increased arterial blood pressure.

## RECENT INSIGHTS

The evidence that long-term exposure to ambient PM<sub>2.5</sub> is an important risk factor of hypertension is further strengthened (55–57). Ambient air pollution and blood pressure are positively related, especially in men, Asians, North Americans, and in areas with higher air pollutant levels (55,56). Consistent with this observation, long-term residential exposures to air pollution and noise are associated with increased incidence of self-reported hypertension in large European cohorts (57). Ambient particulate matter has been consistently associated with gestational hypertension and high blood pressure in childhood (58–60). Finally, PM exposure activates the hypothalamus–pituitary–adrenal and sympathetic–adrenal–medullary axes (61), while short-term reductions in stress hormone following indoor air purification are likely pertinent to the observation that smoke-free air law reduces acute myocardial infarction hospitalization in the United States (62).

## SUMMARY

There is mounting evidence that air pollution increases blood pressure. Given its ubiquitous nature, even modest effects on blood pressure may translate into sizable rises in cardiovascular events at a population level. Even modest rises in nitrogen and sulphur oxides, as well as in PM, enhance consultations for hypertensive emergencies. In addition, delayed rises in blood pressure have been observed in several other studies, with some evidence that hypertensive patients could be more prone to demonstrate a rise in blood pressure unless they take antihypertensive medications.

## CONCLUSIONS

In this chapter, we have reviewed evidence that acute exposure to stressful events increases the incidence of cardiovascular events and may even induce a rare condition of reversible cardiomyopathy. A chronic stressful environment at work or in family life or both is a risk factor for cardiovascular disease, but its causative effect on the development of sustained hypertension is not demonstrated. Other important psychosocial cardiovascular factors are low socioeconomic status, lack of social support, depression, anxiety, hostility and the type D personality. Another emerging cardiovascular risk factor is air pollution, which acts through a variety of mechanisms to increase blood pressure and alter endothelial function. A common and somewhat disappointing feature of these cardiovascular risk factors is that they are not easily reversible, at least at this time. Further research is urgently needed to better delineate preventive strategies to fight against these psychosocial and environmental risk factors and determine their effectiveness in reducing the burden of cardiovascular disease.

## REFERENCES

- Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to cardiovascular risk assessment: The ASSIGN score from the Scottish Heart Health Extended Cohort [SHHEC]. *Heart* 2007; 93: 172–176.
- Stringhini S, Sabia S, Shipley M et al. Association of socioeconomic position with health behaviors and mortality. *JAMA* 2010; 303: 1159–1166.
- Tonne C, Schwartz J, Mittleman M et al. Long-term survival after acute myocardial infarction is lower in more deprived neighborhoods. *Circulation* 2005; 111: 3063–3070.
- Albert MA, Glynn RJ, Buring J, Ridker PM. Impact of traditional and novel risk factors on the relationship between socioeconomic status and incident cardiovascular events. *Circulation* 2006; 114: 2619–2626.
- Rahimi AR, Spertus JA, Reid KJ et al. Financial barriers to health care and outcomes after acute myocardial infarction. *JAMA* 2007; 297: 1063–1072.
- Mookadam F, Arthur HM. Social support and its relationship to morbidity and mortality after acute myocardial infarction: Systematic overview. *Arch Intern Med* 2004; 164: 1514–1518.
- Lett HS, Blumenthal JA, Babyak MA et al. Social support and coronary heart disease: Epidemiologic evidence and implications for treatment. *Psychosom Med* 2005; 67: 869–878.
- Eller NH, Netterstrom B, Gyntelberg F et al. Work-related psychosocial factors and the development of ischemic heart disease: A systematic review. *Cardiol Rev* 2009; 17: 83–97.
- De Vogli R, Ferrie JE, Chandola T et al. Unfairness and health: Evidence from the Whitehall II Study. *J Epidemiol Community Health* 2007; 61: 513–518.
- Eaker ED, Sullivan LM, Kelly-Hayes M et al. Marital status, marital strain, and risk of coronary heart disease or total mortality: The Framingham Offspring Study. *Psychosom Med* 2007; 69: 509–513.
- Orth-Gomer K, Wamala SP, Horsten M et al. Marital stress worsens prognosis in women with coronary heart disease: The Stockholm Female Coronary Risk Study. *JAMA* 2000; 284: 3008–3014.
- Rugulies R. Depression as a predictor for coronary heart disease: a review and meta-analysis. *Am J Prev Med* 2002; 23: 51–61.
- Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom Med* 2003; 65: 201–210.
- Nicholson A, Kuper H, Hemingway H. Depression as an aetiological and prognostic factor in coronary heart disease: A meta-analysis of 6362 events among 146,538 participants in 54 observational studies. *Eur Heart J* 2006; 27: 2763–2774.
- Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. *Psychosom Med* 2004; 66: 802–813.
- van Melle JP, de Jonge P, Spijkerman TA, Tijssen JG, Ormel J, van Veldhuisen DJ, van den Brink RH, van den Berg MP. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis. *Psychosom Med* 2004; 66: 814–822.
- Frasere-Smith N, Lesperance F, Gravel G et al. Social support, depression, mortality during the first year after myocardial infarction. *Circulation* 2000; 101: 1919–1924.
- Horsten M, Mittleman MA, Wamala SP et al. Depressive symptoms and lack of social integration in relation to prognosis of CHD in middle-aged women. The Stockholm Female Coronary Risk Study. *Eur Heart J* 2000; 21: 1072–1080.
- Denollet J, Schiffer AA, Spek V. A general propensity to psychological distress affects cardiovascular outcomes: Evidence from research on the type D [distressed] personality profile. *Circ Cardiovasc Qual Outcomes* 2010; 3: 546–557.
- Smoller JW, Pollack MH, Wassertheil-Smoller S et al. Panic attacks and risk of incident cardiovascular events among postmenopausal women in the Women's Health Initiative Observational Study. *Arch Gen Psychiatry* 2007; 64: 1153–1160.
- Chen YH, Tsai SY, Lee HC, Lin HC. Increased risk of acute myocardial infarction for patients with panic disorder: A nationwide population-based study. *Psychosom Med* 2009; 71: 798–804.
- Frasere-Smith N, Lesperance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. *Arch Gen Psychiatry* 2008; 65: 62–71.
- Shibeshi WA, Young-Xu Y, Blatt CM. Anxiety worsens prognosis in patients with coronary artery disease. *J Am Coll Cardiol* 2007; 49: 2021–2027.
- Szekely A, Balog P, Benko E et al. Anxiety predicts mortality and morbidity after coronary artery and valve surgery—a 4-year follow-up study. *Psychosom Med* 2007; 69: 625–631.

25. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: A meta-analysis. *J Am Coll Cardiol* 2010; 56: 38–46.
26. Roest AM, Martens EJ, Denollet J, de Jonge P. Prognostic association of anxiety post myocardial infarction with mortality and new cardiac events: A meta-analysis. *Psychosom Med* 2010; 72: 563–569.
27. Chida Y, Steptoe A. The association of anger and hostility with future coronary heart disease: A meta-analytic review of prospective evidence. *J Am Coll Cardiol* 2009; 53: 936–946.
28. Denollet J, Gidron Y, Vrints CJ, Conraads VM. Anger, suppressed anger, and risk of adverse events in patients with coronary artery disease. *Am J Cardiol* 2010; 105: 1555–1560.
29. Dupre ME, Nelson A, Lynch SM et al. Socioeconomic, psychosocial, and behavioral characteristics of patients hospitalized with cardiovascular disease. *Am J Med Sci* 2017; 354(6): 565–572.
30. Kivimäki M et al. Job strain as a risk factor for coronary heart disease: A collaborative meta-analysis of individual participant data. *Lancet* 2012; 380: 1491–1497.
31. Yusuf S et al. Blood-pressure and cholesterol lowering in persons without cardiovascular disease. *N Engl J Med* 2016; 374: 2032–2043.
32. Richards SH, Anderson L, Jenkinson CE et al. Psychological interventions for coronary heart disease: Cochrane systematic review and meta-analysis. *Eur J Prev Cardiol* 2018; 25(3): 247–259.
33. Brook RD, Rajagopalan S, Pope CA 3rd et al. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation* 2010; 121(21): 2331–2378.
34. Bartoli CR, Wellenius GA, Diaz EA et al. Mechanisms of inhaled fine particulate air pollution-induced arterial blood pressure changes. *Environ Health Perspect* 2009; 117(3): 361–366.
35. Sun Q, Yue P, Ying Z et al. Air pollution exposure potentiates hypertension through reactive oxygen species-mediated activation of Rho/ROCK. *Arterioscler Thromb Vasc Biol* 2008; 28(10): 1760–1766.
36. Liu L, Ruddy TD, Dalipaj M et al. Influence of personal exposure to particulate air pollution on cardiovascular physiology and biomarkers of inflammation and oxidative stress in subjects with diabetes. *J Occup Environ Med* 2007; 49: 258–265.
37. Rundell KW, Hoffman JR, Caviston R et al. Inhalation of ultrafine and fine particulate matter disrupts systemic vascular function. *Inhal Toxicol* 2007; 19: 133–140.
38. Bräuner EV, Forchhammer L, Möller P et al. Indoor particles affect vascular function in the aged: An air filtration-based intervention study. *Am J Respir Crit Care Med* 2008; 177: 419–425.
39. Adamopoulos D, Vyssoulis G, Karpanou E et al. Environmental determinants of blood pressure, arterial stiffness, and central hemodynamics. *J Hypertens* 2010; 28(5): 903–909.
40. Argacha JF, Adamopoulos D, Gujic M et al. Acute effects of passive smoking on peripheral vascular function. *Hypertension* 2008; 51(6): 1506–1511.
41. Simonetti GD, Schwertz R, Klett M et al. Determinants of blood pressure in preschool children: The role of parental smoking. *Circulation* 2011; 123(3): 292–298.
42. Brook RD, Rajagopalan S. Particulate matter, air pollution, and blood pressure. *J Am Soc Hypertens* 2009; 3(5): 332–350.
43. Urch B, Silverman F, Corey P et al. Acute blood pressure responses in healthy adults during controlled air pollution exposures. *Environ Health Perspect* 2005; 113: 1052–1055.
44. Szyszkowicz M, Rowe BH, Brook RD. Even low levels of ambient air pollutants are associated with increased emergency department visits for hypertension. *Can J Cardiol* 2012; 28(3): 360–366.
45. Guo Y, Tong S, Zhang Y et al. The relationship between particulate air pollution and emergency hospital visits for hypertension in Beijing, China. *Sci Total Environ* 2010; 408(20): 4446–4450.
46. Arbex MA, Saldiva PH, Pereira LA, Braga AL. Impact of outdoor biomass air pollution on hypertension hospital admissions. *J Epidemiol Community Health* 2010; 64(7): 573–579.
47. Johnson D, Parker JD. Air pollution exposure and self-reported cardio-vascular disease. *Environ Res* 2009; 109: 582–589.
48. Van Hee VC, Adar SD, Szpiro AA et al. Exposure to traffic and left ventricular mass and function: The Multi-Ethnic Study of Atherosclerosis. *Am J Respir Crit Care Med* 2009; 179: 827–834.
49. Zanutti A, Canner MJ, Stone PH et al. Ambient pollution and blood pressure in cardiac rehabilitation patients. *Circulation* 2004; 110(15): 2184–2189.
50. Choi JH, Xu QS, Park SY et al. Seasonal variation of effect of air pollution on blood pressure. *J Epidemiol Community Health* 2007; 61(4): 314–318.
51. Auchincloss AH, Diez Roux AV, Dvorchak JT et al. Associations between recent exposure to ambient fine particulate matter and blood pressure in the Multi-ethnic Study of Atherosclerosis [MESA]. *Environ Health Perspect* 2008; 116(4): 486–491.
52. Dvorchak JT, Kannan S, Schulz AJ et al. Acute effects of ambient particulate matter on blood pressure: Differential effects across urban communities. *Hypertension* 2009; 53(5): 853–859.
53. Nawrot T, Perez L, Kunzli N et al. Public health importance of triggers of myocardial infarction: A comparative risk assessment. *Lancet* 2011; 377: 732–740.
54. Fuks K, Moebus S, Hertel S et al. Long-term urban particulate air pollution, traffic noise, and arterial blood pressure. *Environ Health Perspect* 2011; 119(12): 1706–1711.
55. Yang BY, Qian Z, Howard SW et al. Global association between ambient air pollution and blood pressure: A systematic review and meta-analysis. *Environ Pollut* 2018; 235: 576–588.
56. Lin H, Guo Y, Zheng Y et al. Long-term effects of ambient PM<sub>2.5</sub> on hypertension and blood pressure and attributable risk among older Chinese adults. *Hypertension* 2017; 69(5): 806–812.
57. Fuks KB, Weinmayr G, Basagaña X et al. Long-term exposure to ambient air pollution and traffic noise and incident hypertension in seven cohorts of the European study of cohorts for air pollution effects (ESCAPE). *Eur Heart J* 2017; 38(13): 983–990.
58. Zhu Y, Zhang C, Liu D et al. Ambient air pollution and risk of gestational hypertension. *Am J Epidemiol* 2017; 186(3): 334–343.
59. Xue T, Zhu T, Lin W, Talbot EO. Association between hypertensive disorders in pregnancy and particulate matter in the contiguous United States, 1999–2004. *Hypertension* 2018; 72(1): 77–84.
60. Zhang M, Mueller NT, Wang H et al. Maternal exposure to ambient particulate matter  $\leq 2.5 \mu\text{m}$  during pregnancy and the risk for high blood pressure in childhood. *Hypertension* 2018; 72(1): 194–201.
61. Li H, Cai J, Chen R et al. Particulate matter exposure and stress hormone levels: A randomized, double-blind, crossover trial of air purification. *Circulation* 2017; 136(7): 618–627.
62. Weaver AM, Wang Y, Rupp K, Watson DP. Effects of smoke-free air law on acute myocardial infarction hospitalization in Indianapolis and Marion County, Indiana. *BMC Public Health* 2018; 18(1): 232.



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# SERUM URIC ACID, BLOOD PRESSURE AND HYPERTENSION

# 19

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## INTRODUCTION

In the last century we observed a dramatic increase in the prevalence of conditions such as obesity, hypertension and diabetes affecting a large proportion of the adult population living in the industrialized world (1–3). The same trend has also been described in the adolescent population, with a marked increase in the rate of high blood pressure, metabolic syndrome and diabetes leading to premature target-organ damage and cardiovascular diseases (4–5). This chapter is dedicated to the relationship between serum uric acid (SUA) and hypertension with the aim of increasing the level of information about a disease that currently affects a large percentage of the population of all ages.

## URIC ACID: GENERAL CONSIDERATIONS AND BIOLOGICAL ACTIVITIES

Uric acid is the end-product of purine metabolism and circulates in the blood where it is responsible for gout and kidney stones (6). Uric acid is produced by xanthine oxidase (XO) from xanthine and hypoxanthine (7) (Figure 19.1). In the large majority of nonhuman mammals, the levels of SUA are relatively low (1–3 mg/dL) due to the activity of uricase, which degrades uric acid to allantoin. A genetic mutation that occurred about 50 million years ago has deleted uricase from the genome of humans and great apes, leading to an elevation of SUA levels that has progressively increased over time (9). In men, uric acid levels are usually between 4 and 6 mg/dL, with primary excretion through the urine (two-thirds) and the gut (one-third) (8). The exogenous sources of uric acid are the intake of purinergic foods (mainly beer, shellfish and organ meat, and fructose-containing sugars [sucrose and high-fructose corn syrup]) (10,11). Hyperuricaemia can develop as a result of increased production of uric acid from nucleotide turnover (inherited enzyme defects, myeloproliferative disorders and malignancies, diet, etc.) or as a consequence of reduced removal by the kidneys (chronic renal failure, insulin resistance, diuretics, low-dose aspirin, etc.) or mediated by gene polymorphisms controlling

urate excretion or production (12). An increase in SUA can also result as the consequence of the overactivity of the enzyme xanthine-oxidoreductase (XOR) even in presence of average levels of purine load (13) (Figure 19.2). Under normal circumstances, uric acid (as hydrogen urate) may have an antioxidant effect that accounts for as much as 50% of the total serum antioxidant activity (14). However, the same uric acid can also have pro-oxidant effects in the presence of decreased levels of the other serum antioxidants (e.g. vitamin C) (8,15). When uric acid is produced by reactive oxygen species are also generated and largely contribute to the overall burden of oxidative stress (15) with possible negative cardiovascular effects that can be prevented by xanthine-oxidase inhibitors (16–18). Uric acid has been shown to cause also intracellular oxidative stress in a variety of cell types (adipocytes, hepatocytes, myocytes, endothelial cells, etc.) as a consequence of the stimulation of NADPH oxidase resulting in mitochondrial oxidative stress (19–21). The reactive oxygen species associated with uric acid production may interfere with the biological activity of nitric oxide leading to a series of negative cardiovascular and metabolic effects (8,15). In addition, uric acid has been shown to induce the expression of platelet-derived growth factor  $\alpha$  (PDGF- $\alpha$ ) and PDGF- $\alpha$  receptor, thereby stimulating the proliferation of vascular smooth muscle cells (22,23). In vascular endothelial cells, uric acid stimulates the expression of cyclooxygenase-2, with subsequent increase in local thromboxane production, as well as the expression of monocyte chemoattractant protein-1 (MCP-1), which has been implicated in the pathogenesis of atherosclerosis (15,24). In particular, uric acid activates the renin-angiotensin system by stimulating the expression of angiotensinogen, angiotensin-converting enzyme and angiotensin II receptors, and increasing the levels of angiotensin II (25). Uric acid also upregulates the expression of C-reactive protein (26) and induces a pro-inflammatory expression profile, characterised by increased expression of interleukin-1 $\beta$ , interleukin-6 and tumour necrosis factor- $\alpha$  (8). While the precise details of some of these processes remain under investigation, most of the available data support the combined role of uric acid and its production as a functional step of a mechanistic pathway leading to hypertension, atherosclerosis and target-organ damage.



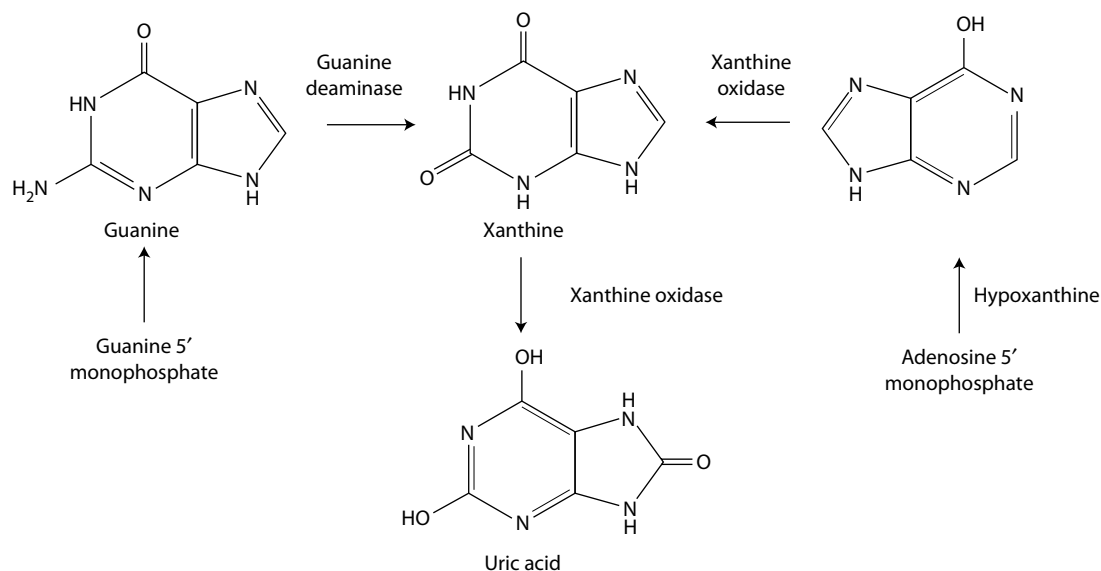


**Figure 19.1** Biochemical pathway involved in SUA production. (Adapted from Dawson J et al. *Curr Med Chem* 2007; 14(17): 1879–1886.)

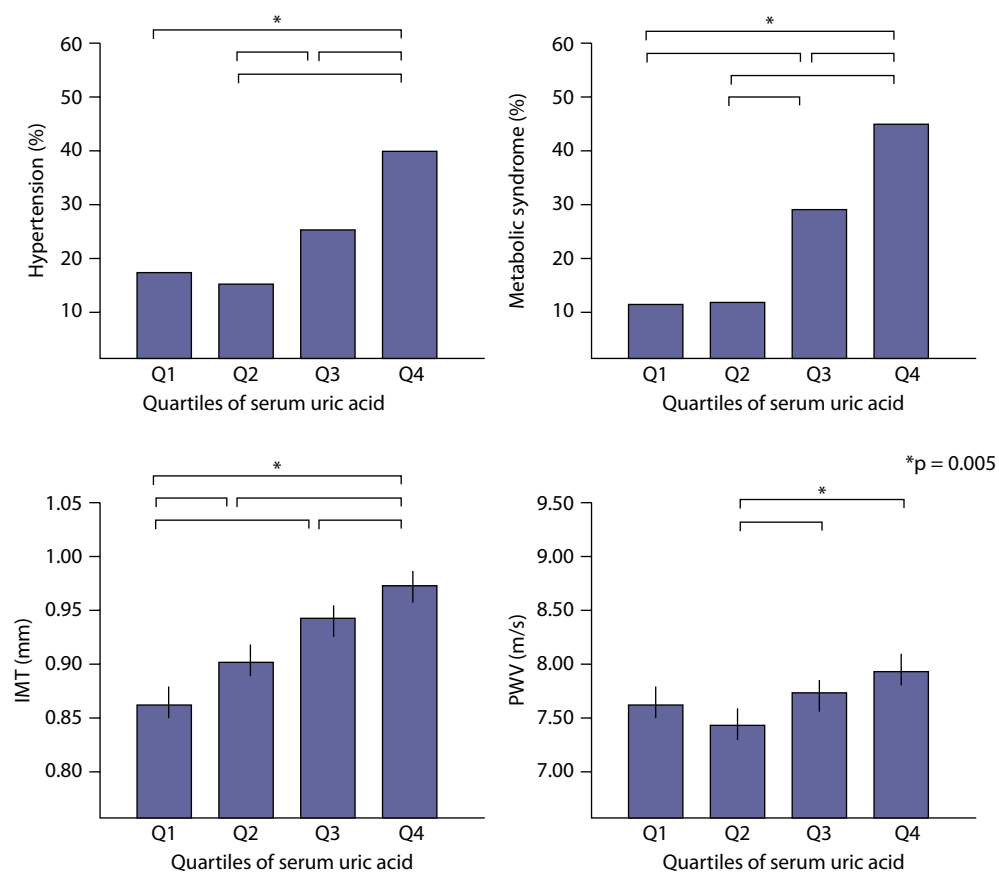


**Figure 19.2** Schematic summary of the main pathways involved in SUA production, plasma levels and cardiovascular disease.

## URIC ACID AND CV DISEASE: EPIDEMIOLOGICAL CONSIDERATIONS

From the epidemiological point of view and increased uric acid levels has been reported in patients with gout, but also in a very large population of subjects with asymptomatic hyperuricemia whose prevalence is almost eightfold higher when compared to patients bearing gout (27). This has important clinical implications since asymptomatic hyperuricemia is probably associated with an increased risk of cardiovascular, renal and metabolic diseases (28,29) and should be considered in the overall assessment of patients beyond the presence of gout.

A close association between elevated SUA and cardiovascular disease was already known since the late nineteenth century (30) when Alexander Heig published a seminal paper on the causative role of SUA in the development of hypertension and renal disease. In particular elevations of serum uric acid are common in subjects with hypertension, obesity, metabolic syndrome, type 2 diabetes, chronic kidney disease, and heart disease (31). Despite such evidence, SUA it is not routinely measured in subjects at cardiovascular risk, and management of asymptomatic hyperuricemia is not currently recommended (32,33). Many studies strongly suggest a close relationship between SUA and arterial hypertension both in experimental and clinical conditions, raising the possibility that elevated uric acid level may be directly involved in the pathogenesis of elevated blood pressure (28,34,35).

## URIC ACID AND HYPERTENSION

### EXPERIMENTAL STUDIES

Beside the epidemiological evidence relating elevated uric acid with the presence of hypertension the role of uric acid in hypertension is supported by some experimental data in animals that developed hyperuricemia and hypertension in response to a treatment with an uricase inhibitor (36). In this animal setting, hypertension developed in two phases. A reversible one, mediated by a salt-insensitive uric acid – dependent activation of the renin-angiotensin system and leading to oxidative stress and the development of endothelial dysfunction. This was followed by and a second phase where the hypertension became kidney dependent and salt sensitive and persisted despite the return of uric acid levels to baseline values (37). The hemodynamic and renal abnormalities observed in rats were largely comparable to those observed in human hypertension particular at the renal level where the oxidative stress associated with hyperuricemia can lead to a marked vasoconstriction of the afferent arteriole associated with a preserved glomerular filtration rate (38). Furthermore, uric acid was recently found to enter cells via specific transporters (34). Intracellular uric acid could activate signaling mechanisms that stimulates the release of inflammatory mediators, vasoconstrictive substances, proliferative growth factors, and oxidants (22,24,34,37) and induce mitochondrial dysfunction (39). This pro-oxidant effect cannot be counterbalanced by the presumed

antioxidant effects of circulating uric acid and this results in a generalized pro-oxidative status that is responsible for the negative effects of hyperuricemia.

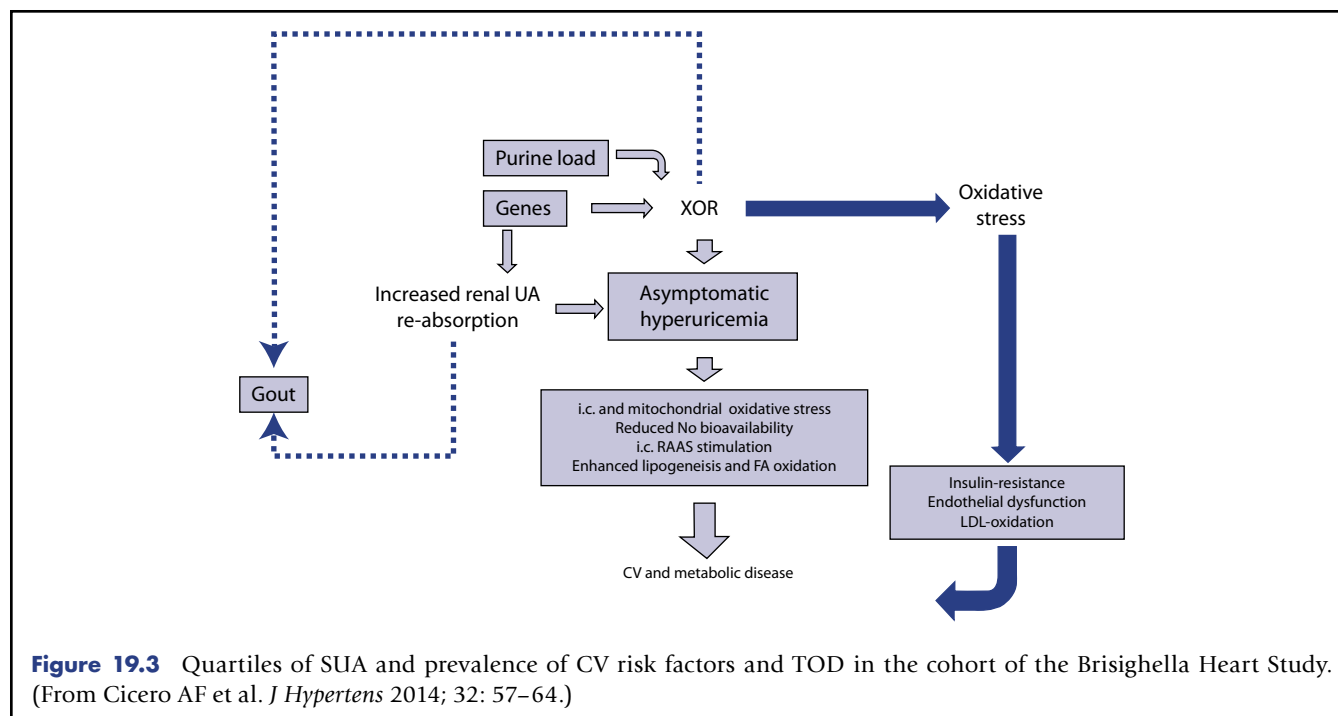
### HYPERURICAEMIA AS A RISK FACTOR FOR HYPERTENSION

A close relationship between serum uric acid and hypertension has been demonstrated also in humans independently on the traditional cardiovascular risk factors including age, obesity, hypercholesterolaemia, hypertriglyceridaemia, low high-density lipoprotein cholesterol, diabetes, family history of hypertension, smoking and alcohol consumption (21). Increased serum uric acid can be also associated with the presence of hypertension in children. Among children recently diagnosed with primary hypertension, 89% have elevated SUA concentrations, while this occurs in only 30% of those diagnosed with secondary hypertension and 0% of children with normal blood pressure (40).

The close correlation between the increased levels of SUA and hypertension has been clearly supported by two different meta-analyses of epidemiological studies carried out in different populations of subjects. In the first meta-analysis of 18 prospective studies that included 55,607 participants with baseline normal blood pressure, hyperuricaemia was associated with an increased risk of incident hypertension (41). Another meta-analysis of 25 prospective and retrospective studies and 97,824 participants concluded that hyperuricaemia was a predictive factor for developing hypertension, independently of sex and ethnicity (Asian vs. non-Asian) (42).

The results have been confirmed also by the results of the Brisighella Heart Study (35) (Figure 19.3) and the Pamela Study (43) showing a significant increase in the relative risk of new-onset hypertension in subjects with SUA levels above the average value of the population. An elevated uric acid level predicts hypertension also in childhood and adolescence (44). The National Health and Nutrition Examination Survey (1999–2006) involving more than 6000 adolescents (12–17 years old) found a 38% increase in the risk of hypertension for every 1.0 mg/dL change in uric acid level (45). This predictive role of elevated SUA levels is completely lost in the elderly population (46). A significant increase in SUA has been described in subjects with pre-hypertension (47–49), new-onset hypertension, gestational hypertension (50) whereas uric acid was not elevated in secondary hypertension unless a significant decrease of renal function develops. A recent paper published by Kuwabara et al. (51), demonstrated that hyperuricemia can contribute to the progression from pre-hypertension to established hypertension in subjects without concomitant risk factors. The SUA concentrations are also higher in women with pre-eclampsia than in healthy pregnant women and in patients with non-hypertensive maternal and fetal complications (52). Furthermore, the presence of hyperuricemia during the fetal life may increase the risk of hypertension in the adult life, particularly for those subjects with low birth weight (8,53).

From the pathogenetic point of view, the crucial point is the identification of the threshold level of SUA that is associated with an increased relative risk of hypertension



in the normotensive or pre-hypertensive population (54). Most of the studies has considered as a risk factor circulating uric acid levels above 7 mg/dL currently adopted in the management of gout. Conversely, some degree of cardiovascular involvement can be already demonstrated for SUA levels significantly lower and considered in the normal range (from 4.5 to 6.0 mg/dL). In exposed populations, the risk of primary hypertension increased significantly starting from SUA levels of 5.5 mg/dL (40,45) and supports the option that the cardiovascular effects of SUA do not necessarily involve urate deposition.

### HYPERURICAEMIA IN PATIENTS WITH HYPERTENSION

The connection between hyperuricaemia and hypertension has been known for over a century (30). Hyperuricaemia is found in 25% of individuals with untreated hypertension and three-quarters of patients with malignant hypertension (55). The prevalence of hyperuricaemia has been found to be higher in people with more severe hypertension (56). In patients treated for hypertension, hyperuricaemia is associated with an increased risk of uncontrolled hypertension (57). In addition, hyperuricaemia has also been reported to be associated with resistance to antihypertensive treatment (58).

### HYPERURICAEMIA, HYPERTENSION AND CARDIOVASCULAR DISEASE

Despite the earlier studies tended to conclude that elevated uric acid levels were only a marker of cardiovascular risk without any predictive role (59–61), more recent evidence have supported a causative relationship in hypertensive patients that remained robust and after adjustment for

potential confounders (62). In particular increased SUA concentrations were found to be a risk factor for severity of coronary artery disease (63), atrial fibrillation (64), myocardial infarction, stroke (65) and heart failure (66).

### TREATMENT OF HYPERURICEMIA AND HYPERTENSION

The considerable amount of evidence supporting a close correlation between elevated levels of SUA and hypertension can have important therapeutic implications particularly for xanthine-oxidase inhibitors (67). At present, only a limited number of studies have investigated the effects of urate lowering drugs in patients with hyperuricemia and elevated blood pressure reporting variable results depending on the characteristics of the patient populations and the designs of the studies. The complexity of the mechanisms involved in the increase in SUA (overproduction vs. under-excretion) and the lack of control of concomitant risk factors affecting blood pressure (e.g. use of diuretics) are probably responsible for the differences in the results of the interventional studies and conclusive results are awaited from the clinical trials currently ongoing in this area (Table 19.1).

### PRE-HYPERTENSION OR STAGE 1 HYPERTENSION

Pilot studies suggest that lowering uric acid can result in an improvement in blood pressure in obese adolescents with hyperuricemia and pre-hypertension (68), in adolescents with newly diagnosed hypertension (69), and in adults with asymptomatic hyperuricemia (70,71). Soletsky et al. (70), have investigated a group of obese pre-hypertensive

**Table 19.1** Summary of randomized clinical trials in the field of urate-lowering treatment and cardiovascular disease

| CV field                                  | Intervention               | Primary outcomes                                      | ID No. and status                                                     |
|-------------------------------------------|----------------------------|-------------------------------------------------------|-----------------------------------------------------------------------|
| BP control                                | Febuxostat vs. allopurinol | Clinic BP and ABPM                                    | NCT01701622 <sup>a</sup> ; terminated (unable to enroll participants) |
| Coronary endothelial dysfunction          | Febuxostat vs. placebo     | Coronary flow                                         | NCT01763996 <sup>a</sup> ; completed                                  |
| BP control                                | Febuxostat vs. placebo     | ABPM                                                  | NCT01496469 <sup>a</sup> ; completed                                  |
| Exercise tolerance in chronic angina      | Febuxostat vs. placebo     | ETT                                                   | NCT01549977 <sup>a</sup> ; terminated                                 |
| Vascular structure and function (FORWARD) | Febuxostat vs. allopurinol | Carotid-femoral PWV                                   | EudraCT 2014-5567-33; enrollment closed                               |
| New on set metabolic syndrome (FAST)      | Febuxostat vs. placebo     | Insulin resistance and features of metabolic syndrome | NCT01654276 <sup>a</sup> ; ongoing                                    |
| BP and CV complications (CARES)           | Febuxostat vs. allopurinol | MACE                                                  | NCT01101035 <sup>a</sup> ; ongoing                                    |
| Treatment of CHD (ALL-HEARTY)             | Allopurinol vs. placebo    | MACE                                                  | EudraCT 2013-003559-39; ongoing                                       |
| Cerebrovascular protection (XILO-FIST)    | Allopurinol vs. placebo    | White matter protection                               | NCT02122718 <sup>a</sup> ; starting recruitment                       |
| Major CV diseases (FREED)                 | Febuxostat vs. placebo     | MACE                                                  | NCT01984749 <sup>a</sup> ; ongoing                                    |

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CHD, coronary heart disease; CV, cardiovascular; ETT, exercise tolerance testing; MACE, major adverse cardiovascular events; PWV, pulse wave velocity.

<sup>a</sup>ClinicalTrials.gov.

adolescents showing that both a xanthine-oxidase inhibitor (allopurinol) or an uricosuric agent (probenecid) had a significant effect on ambulatory systolic and diastolic blood pressure. In another study, Feig et al. (69) investigated the effects of urate-lowering treatment in 30 adolescents with newly diagnosed stage 1 essential hypertension reporting a significant reduction in blood pressure only in response to allopurinol.

## ESTABLISHED HYPERTENSIVE PATIENTS

Uric acid-lowering treatment has been shown to reduce blood pressure also in patients with established hypertension. The UK Clinical Practice Research Datalink involving 365 elderly patients with hypertension and 6678 controls, found that the treatment with allopurinol was associated with significant reductions in both systolic and diastolic blood pressure (72). The efficacy of another X inhibitor, febuxostat, was evaluated by Gunawardhana et al. (74), in a phase II, randomised, double-blind, placebo-controlled study of 121 patients with hypertension and hyperuricaemia. At week 6, there were no significant differences between the febuxostat and the placebo group in the 24-hour mean ambulatory systolic blood pressure. However, a pre-specified subgroup analysis systolic blood pressure was significantly reduced after 6 weeks of treatment in patients with normal renal function (73). A comprehensive meta-analysis of both prospective and retrospective studies carried out by Agrawal et al. (75), evaluated the effects of allopurinol treatment on blood pressure in 10 studies involving 738 patients. In this analysis allopurinol significantly reduced systolic and diastolic

pressure compared with the control group with a substantial homogeneity across the studies despite a remarkable difference in the characteristics of the study populations.

## PREVENTION OF CARDIOVASCULAR EVENTS

A comprehensive population study has demonstrated that the treatment with allopurinol is associated with an improved survival in the general population including patients with hypertension (75). In hypertensive patients a retrospective study reported decreased incidence of stroke and cardiovascular in response to allopurinol (76). The favourable effect was greater in patients treated with the higher dose of allopurinol, confirming the importance of XO inhibition in patients with hypertension. These results are in agreement with those of a systematic review and meta-analysis reporting that treatment with XO inhibitors improved endothelial function, circulating oxidative stress markers and cardiovascular prognosis in patients with or at risk of cardiovascular disease (77,78).

## CONCLUSIONS

A large number of experimental and clinical studies suggest that uric acid may be actively involved in the complex pathophysiological pathway leading to hypertension. Hyperuricaemia is the consequence of several dietary and genetic factors leading to stimulation of XO activity and oxidative stress. A causality role for uric acid in hypertension is supported by experimental and clinical studies as

well as by some preliminary therapeutic evidence involving XO inhibitors. Whether or not this evidence will be confirmed by other ongoing studies, the increase in the amount of research focused on the role of uric acid in hypertension has provided new insights into the management of hypertension and related cardiovascular diseases.

## REFERENCES

- Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988–2008. *JAMA* 2010; 303: 2043–2050.
- Danaei G, Friedman AB, Oza S et al. Diabetes prevalence and diagnosis in US states: Analysis of health surveys. *Popul Health Metr* 2009; 7: 16.
- Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. *JAMA* 2010; 303: 235–241.
- Pacifico L, Nobili V, Anania C et al. Pediatric nonalcoholic fatty liver disease, metabolic syndrome and cardiovascular risk. *World J Gastroenterol* 2011; 17: 3082–3091.
- Nadeau KJ, Maahs DM, Daniels SR, Eckel RH. Childhood obesity and cardiovascular disease: Links and prevention strategies. *Nat Rev Cardiol* 2011; 8: 513–525.
- Becker MA. Hyperuricemia. In: Lang F (ed.) *Encyclopedia of Molecular Mechanisms of Disease*. Springer Berlin Heidelberg, Berlin, Heidelberg; 2009: 956.
- Dawson J, Quinn T, Walters M. Uric acid reduction: A new paradigm in the management of cardiovascular risk? *Curr Med Chem* 2007; 14(17): 1879–1886.
- Baillie JK, Bates MG, Thompson AA et al. Endogenous urate production augments plasma antioxidant capacity in healthy lowland subjects exposed to high altitude. *Chest* 2007; 131: 1473–1478.
- Johnson RJ, Kang DH, Feig D et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension* 2003; 41: 1183–1190.
- Johnson RJ, Tittle S, Cade JR et al. Uric acid, evolution and primitive cultures. *Semin Nephrol* 2005; 25: 3–8.
- Nicholls A, Snaith ML, Scott JT. Effect of oestrogen therapy on plasma and urinary levels of uric acid. *Br Med J* 1973; 1: 449–451.
- Rho YH, Zhu Y, Choi HK. The epidemiology of uric acid and fructose. *Semin Nephrol* 2011; 31: 410–419.
- Paul BJ, Anoopkumar K, Krishnan V. Asymptomatic hyperuricemia: Is it time to intervene? *Clin Rheumatol* 2017; 36(12): 2637–2644.
- Berry CE, Hare JM. Xanthine oxidoreductase and cardiovascular disease: Molecular mechanisms and pathophysiological implications. *J Physiol* 2004; 555(Pt 3): 589–606.
- Maxwell SR, Thomason H, Sandler D et al. Antioxidant status in patients with uncomplicated insulin-dependent and non-insulin-dependent diabetes mellitus. *Eur J Clin Invest* 1997; 27: 484–490.
- Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. *Semin Nephrol* 2005; 25: 39–42.
- Butler R, Morris AD, Belch JJ et al. Allopurinol normalizes endothelial dysfunction in type 2 diabetics with mild hypertension. *Hypertension* 2000; 35: 746–751.
- Farquharson CA, Butler R, Hill A et al. Allopurinol improves endothelial dysfunction in chronic heart failure. *Circulation* 2002; 106: 221–226.
- Doehner W, Schoene N, Rauchhaus M et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: Results from 2 placebo-controlled studies. *Circulation* 2002; 105: 2619–2624.
- Sautin YY, Nakagawa T, Zharikov S, Johnson RJ. Adverse effects of the classic antioxidant uric acid in adipocytes: NADPH oxidase-mediated oxidative/nitrosative stress. *Am J Physiol Cell Physiol* 2007; 293: C584–C596.
- Lanaspa MA, Sanchez-Lozada LG, Choi YJ et al. Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: Potential role in fructose-dependent and -independent fatty liver. *J Biol Chem* 2012; 287: 40732–40744.
- Choi YJ, Shin HS, Choi HS et al. Uric acid induces fat accumulation via generation of endoplasmic reticulum stress and SREBP-1c activation in hepatocytes. *Lab Invest* 2014; 94: 1114–1125.
- Rao GN, Corson MA, Berk BC. Uric acid stimulates vascular smooth muscle cell proliferation by increasing platelet-derived growth factor A-chain expression. *J Biol Chem* 1991; 266: 8604–8608.
- Mustard JF, Murphy EA, Ogryzlo MA, Smythe HA. Blood coagulation and platelet economy in subjects with primary gout. *CMAJ* 1963; 89: 1207–1211.
- Kanellis J, Watanabe S, Li JH et al. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. *Hypertension* 2003; 41: 1287–1293.
- Yu MA, Sanchez-Lozada LG, Johnson RJ, Kang DH. Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. *J Hypertens* 2010; 28: 1234–1242.
- Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid-induced C-reactive protein expression: Implication on cell proliferation and nitric oxide production of human vascular cells. *J Am Soc Nephrol* 2005; 16: 3553–3562.
- Trifiro G, Morabito P, Cavagna L et al. Epidemiology of gout and hyperuricaemia in Italy during the years 2005–2009: A nationwide population-based study. *Ann Rheum Dis* 2013; 72: 694–700.
- Borghi C, Agabiti-Rosei E, Bardin T et al. Serum uric acid and the risk of cardiovascular and renal disease. *J Hypertens* 2015; 33: 1729–1741.
- Johnson RJ, Bakris GL, Borghi C et al. Hyperuricemia, acute and chronic kidney disease, hypertension, and cardiovascular disease: Report of a scientific workshop organized by the National Kidney Foundation. *Am J Kidney Dis* 2018; 71(6): 851–865.
- Van Pelt GW. A study of Haig's uric acid theory. *Boston Med Surg J* 1896; 134: 129–134.
- Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med* 2008; 359: 1811–1821.
- Dincer HE, Dincer AP, Levinson DJ. Asymptomatic hyperuricemia: To treat or not to treat. *Cleve Clin J Med* 2002; 69: 594.
- Neogi T. Asymptomatic hyperuricemia: Perhaps not so benign? *J Rheumatol* 2008; 35: 734–737.
- Feig DI, Madero M, Jalal DI et al. Uric acid and the origins of hypertension. *J Pediatr* 2013; 162: 896–902.
- Cicero AF, Salvi P, D'Addato S et al. Association between serum uric acid, hypertension, vascular stiffness and subclinical atherosclerosis: Data from the Brisighella Heart Study. *J Hypertens* 2014; 32: 57–64.
- Mazzali M, Hughes J, Kim YG et al. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension* 2001; 38: 1101–1106.
- Watanabe S, Kang DH, Feng L et al. Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. *Hypertension* 2002; 40: 355–360.
- Sanchez-Lozada LG, Tapia E, Avila-Casado C et al. Mild hyperuricemia induces glomerular hypertension in normal rats. *Am J Physiol* 2002; 283: F1105–F1110.
- Johnson RJ, Feig DI, Herrera-Acosta J, Kang DH. Resurrection of uric acid as a causal risk factor in essential hypertension. *Hypertension* 2005; 45(1): 18–20.
- Feig DI, Johnson RJ. Hyperuricemia in childhood primary hypertension. *Hypertension* 2003; 42: 247–252.
- Grayson PC, Kim SY, Lavalley M, Choi HK. Hyperuricemia and incident hypertension: A systematic review and meta-analysis. *Arthritis Care Res (Hoboken)* 2011; 63: 102–110.
- Zhang W, Sun K, Yang Y et al. Plasma uric acid and hypertension in a Chinese community: Prospective study and meta-analysis. *Clin Chem* 2009; 55: 2026–2034.
- Bombelli M, Ronchi I, Volpe M et al. Prognostic value of serum uric acid: New-onset in and out-of-office hypertension and long-term mortality. *J Hypertens* 2014; 32(6): 1237–1244.
- Alper AB Jr, Chen W, Yau L et al. Childhood uric acid predicts adult blood pressure: The Bogalusa Heart Study. *Hypertension* 2005; 45: 34–38.
- Loeffler LF, Navas-Acien A, Brady TM et al. Uric acid level and elevated blood pressure in US adolescents: National Health and Nutrition Examination Survey, 1999–2006. *Hypertension* 2012; 59: 811–817.
- Lu Z, Dong B, Wu H et al. Serum uric acid level in primary hypertension among Chinese nonagenarians/centenarians. *J Hum Hypertens* 2009; 23: 113–121.
- Lee JE, Kim YG, Choi YH et al. Serum uric acid is associated with microalbuminuria in prehypertension. *Hypertension* 2006; 47: 962–967.
- Liang J, Xue Y, Zou C et al. Serum uric acid and prehypertension among Chinese adults. *J Hypertens* 2009; 27: 1761–1765.



50. Syamala S, Li J, Shankar A. Association between serum uric acid and prehypertension among US adults. *J Hypertens* 2007; 25: 1583–1589.
51. Kuwabara M, Hisatome I, Niwa K et al. Uric acid is a strong risk marker for developing hypertension from prehypertension: A 5-year Japanese cohort study. *Hypertension* 2018; 71(1): 78–86.
52. Martin AC, Brown MA. Could uric acid have a pathogenic role in pre-eclampsia? Nature reviews. *Nephrology* 2010; 6: 744–748.
53. Thangaratinam S, Ismail KM, Sharp S, Coomarasamy A, Khan KS. Accuracy of serum uric acid in predicting complications of pre-eclampsia: A systematic review. *BJOG* 2006; 113: 369–378.
54. Barker D, Osmond C, Golding J et al. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ* 1989; 298: 564–567.
55. Desideri G, Castaldo G, Lombardi A et al. Is it time to revise the normal range of serum uric acid levels? *Eur Rev Med Pharmacol Sci* 2014; 18: 1295–1306.
56. Cannon PJ, Stason WB, Demartini FE et al. Hyperuricemia in primary and renal hypertension. *N Engl J Med* 1966; 275: 457–464.
57. Juraschek SP, Kovell LC, Miller ER, Gelber AC. Dose-response association of uncontrolled blood pressure and cardiovascular disease risk factors with hyperuricemia and gout. *PLOS ONE* 2013; 8: e56546.
58. Cicero AF, Rosticci M, Fogacci F et al. High serum uric acid is associated to poorly controlled blood pressure and higher arterial stiffness in hypertensive subjects. *Eur J Intern Med* 2017; 37: 38–42.
59. Borghi C, Tubach F, De Backer G et al. Lack of control of hypertension in primary cardiovascular disease prevention in Europe: Results from the EURIKA study. *Int J Cardiol* 2016; 218: 83–88.
60. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: The Framingham Heart Study. *Ann Intern Med* 1999; 131: 7–13.
61. Moriarty JT, Folsom AR, Iribarren C et al. Serum uric acid and risk of coronary heart disease: Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol* 2000; 10: 136–143.
62. Wheeler JG, Juzwishin KD, Eiriksdottir G et al. Serum uric acid and coronary heart disease in 9,458 incident cases and 155,084 controls: Prospective study and meta-analysis. *PLOS MED* 2005; 2: e76.
63. Borghi C, Rodriguez-Artalejo F, De Backer G et al. The association between blood pressure and lipid levels in Europe: European Study on Cardiovascular Risk Prevention and Management in Usual Daily Practice. *J Hypertens* 2016; 34: 2155–2163.
64. Sinan Deveci O, Kabakci G, Okutucu S et al. The association between serum uric acid level and coronary artery disease. *Int J Clin Pract* 2010; 64: 900–907.
65. Chao TF, Hung CL, Chen SJ et al. The association between hyperuricemia, left atrial size and new-onset atrial fibrillation. *Int J Cardiol* 2013; 168: 4027–4032.
66. Bos MJ, Koudstaal PJ, Hofman A et al. Uric acid is a risk factor for myocardial infarction and stroke: The Rotterdam Study. *Stroke* 2006; 37: 1503–1507.
67. Krishnan E. Hyperuricemia and incident heart failure. *Circ Heart Fail* 2009; 2: 556–562.
68. Borghi C, Desideri G. Urate-lowering drugs and prevention of cardiovascular disease: The emerging role of xanthine oxidase inhibition. *Hypertension* 2016; 67(3): 496–498.
69. Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: A randomized trial. *JAMA* 2008; 300: 924–932.
70. Soletsky B, Feig DI. Uric acid reduction rectifies prehypertension in obese adolescents. *Hypertension* 2012; 60: 1148–1156.
71. Kanbay M, Huddam B, Azak A et al. A randomized study of allopurinol on endothelial function and estimated glomerular filtration rate in asymptomatic hyperuricemic subjects with normal renal function. *Clin J Am Soc Nephrol* 2011; 6: 1887–1894.
72. Kanbay M, Ozkara A, Selcoki Y et al. Effect of treatment of hyperuricemia with allopurinol on blood pressure, creatinine clearance, and proteinuria in patients with normal renal functions. *Int Urol Nephrol* 2007; 39: 1227–1233.
73. Beattie CJ, Fulton RL, Higgins P et al. Allopurinol initiation and change in blood pressure in older adults with hypertension. *Hypertension* 2014; 64: 1102–1107.
74. Gunawardhana L, McLean L, Punzi HA et al. Effect of febuxostat on ambulatory blood pressure in subjects with hyperuricemia and hypertension: A phase 2 randomized placebo-controlled study. *J Am Heart Assoc* 2017; 6(11): e006683.
75. Agarwal V, Hans N, Messerli FH. Effect of allopurinol on blood pressure: A systematic review and meta-analysis. *J Clin Hypertens* 2013; 15: 435–442.
76. Chen JH, Lan JL, Cheng CF et al. Effect of urate-lowering therapy on the risk of cardiovascular disease and all-cause mortality in patients with gout: A case-matched cohort study. *J Rheumatol* 2015; 42(9): 1694–1701.
77. MacIsaac RL, Salatzki J, Higgins P et al. Allopurinol and cardiovascular outcomes in adults with hypertension. *Hypertension* 2016; 67: 535–540.
78. Higgins P, Dawson J, Lees KR et al. Xanthine oxidase inhibition for the treatment of cardiovascular disease: A systematic review and meta-analysis. *Cardiovasc Ther* 2012; 30: 217–226.



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## INTRODUCTION

In the modern approach to cardiovascular (CV) disease management, the role of CV risk factors is of key importance. Early identification and prompt treatment of multiple concomitant risk factors contributes to prevention or delay of CV events and today represents a fundamental step of any preventive strategy for reducing the burden of CV diseases. This consideration relies on the observation that CV risk factors seldom occur alone. In particular, hypertension and dyslipidaemia often coexist, and the concomitance of these conditions exponentially increases the risk of having major CV events during the next 10 years.

Hypertensive patients have a higher prevalence of dyslipidaemia than normotensive individuals with comparable characteristics in terms of age, sex and race. On the other hand, among patients with hypercholesterolemia and hypertriglyceridemia, blood pressure (BP) levels are often above the normal thresholds of 140/90 mmHg (1).

This frequent clustering of hypertension and dyslipidaemia increases the need for a global approach to reduce CV risk, thus overcoming the former classical approach based on a 'silos'-based view of individual risk factors. Such a concept has been a cornerstone and qualifying feature of the latest sets of European Guidelines on hypertension management and control (2).

The pathophysiological basis of the reciprocal pathophysiological consequences of multiple concomitant alterations due to the presence of different CV risk factors in the same individuals is quite solid. Indeed, the endothelium has a pivotal role in the concurrence of hypertension and dyslipidaemia as well as in the pathogenesis of atherosclerotic disease and its complications. Both hypertension and dyslipidaemia may promote endothelial dysfunction, with a loss of normal structure and regulatory function of the vessel walls. The damage induced by oxidized low-density lipoprotein cholesterol (LDL-c) deposition may be responsible for inflammation, leukocyte and platelet adhesion, smooth cell growth and increased synthesis of collagen and fibronectin, that lead to a reduction of nitric oxide production and a consequent impaired vascular relaxation (3). In addition, hypercholesterolemia may amplify the vasoconstrictive effect of endothelin and angiotensin-II, with an increase of vascular resistance and of BP levels. The

association between dyslipidaemia and hypertension may be linked to insulin resistance, but also to inflammation related to abdominal obesity in patients affected by metabolic syndrome (4). Also, renin-angiotensin-aldosterone system (RAAS) may be overactivated in the presence of hypercholesterolemia, and concentrations of angiotensin peptides are increased within atherosclerotic plaques in both experimental and clinical studies (5). This process is self-sustaining because hypertension promotes shear and oxidative stress and enhances endothelial permeability to lipoproteins.

In the present chapter, we briefly discuss the pathophysiological and clinical consequences of dyslipidaemia in hypertensive patients at different CV risk profiles, thus highlighting the need for approaching individual global CV risk profiles rather than reducing absolute levels of BP or plasma cholesterol in asymptomatic subjects at high risk of experiencing major CV events.

## HYPERTENSION, DYSLIPIDEMIA AND ATHEROSCLEROSIS

Essential hypertension promotes the development and accelerates the progression of atherosclerosis at multiple vascular districts, thus favouring the occurrence of major CV events, including myocardial infarction, coronary events, ischaemic stroke and CV death. Hypertension, in turn, may be a secondary and late manifestation of atherosclerotic disease, due to an increased arterial stiffness both in large conduits and in small resistance vessels (6,7).

A prospective study including 2831 normotensive women demonstrated that high levels of total cholesterol and triglycerides and low levels of high-density lipoprotein cholesterol (HDL-c) were associated with an increased risk of developing hypertension, and this risk maintained statistical significance even after corrections for confounding factors in the multivariable analysis. This relationship was confirmed even after excluding patients with diabetes and obesity.

In 3110 normotensive men enrolled in the Physicians' Health Study and followed for 14 years, it was demonstrated that the risk of developing hypertension was

increased by 23% and 39%, in patients with total cholesterol and non-HDL cholesterol levels in the highest quintile, respectively. On the other hand, the risk of becoming hypertensive was decreased by 32% in patients with HDL cholesterol in the highest quintile compared with those in the lowest quintile (8).

In the San Antonio Heart Study, the relative risk of new-onset hypertension was 1.42 in patients with triglyceride levels >110 mg/dL after a 7-year follow up (9).

In a study including 16,130 adult normotensive women, after a 10-year follow up the incidence of hypertension was increased by 14% and 25% in patients with high concentrations of total cholesterol and non-HDL cholesterol, respectively, and decreased by 19% in subjects with high HDL-cholesterol (10). Another study demonstrated that high concentrations of apolipoprotein-B were associated with a 1.4-fold higher risk of hypertension.

In this latter regard, it should be highlighted that other features of dyslipidaemia, including apolipoproteins, should be always considered. As an example, if all the lipid variables were simultaneously analysed in a multiple logistic regression analysis, the risk of hypertension was increased by 2.3-fold in those individuals with high compared with those with low cholesterol levels (11). On the basis of these results, abnormal lipid profile seems to anticipate and predict the future development of hypertension, and particularly its consequences and outcomes.

### TOTAL CARDIOVASCULAR RISK PROFILE IDENTIFICATION, PROGNOSTIC RELEVANCE AND MANAGEMENT

Several observational studies and randomized clinical trials have demonstrated that the net clinical benefit of lipid-lowering therapy depends on baseline individual risk profile, with a more intensive therapeutic approach required in patients with a high- or very-high-risk profile.

As mentioned earlier, according to the current guidelines from European Society of Cardiology (ESC) (12), the assessment of individual risk is a cornerstone of all clinical decisions in terms of diagnosis and treatment strategies. These guidelines suggest the use of the SCORE system (13), which estimates the 10-year risk of CV mortality on the basis of total cholesterol levels, blood pressure, age, sex and smoking habit.

Four categories of risk have been established and related to different therapeutic recommendations: (1) low risk (SCORE  $\leq 1\%$  of 10-year CV mortality): lifestyle education aimed at avoiding the progression of atherosclerotic disease and maintaining a low level of CV risk; (2) moderate risk (SCORE  $\geq 1\% - < 5\%$ ): pharmacological therapy may be evaluated in addition to lifestyle interventions; (3) high risk (SCORE  $\geq 5\% - < 10\%$ ): the beginning of pharmacological therapy is suggested in the absence of contraindications; (4) very high risk ( $\geq 10\%$ ): pharmacological therapy is necessary. It should be also noted, however, that although reproducible, simple, largely applicable and not expensive, this risk score evaluation is limited to individuals aged from 40–65 years and estimates only the risk of mortality, and within the relatively short period of 10 years, not taking into account the long-term probability of death.

For these reasons, ESC guidelines (14) do not recommend treatment decisions based on long-term risk stratification, although this issue will probably need to be revised in the future.

As an example, young people at estimated low 10-year risk (due to their age) but with high levels of other concomitant risk factors are expected to have a high long-term risk of CV morbidity and mortality. In addition, the relatively low levels of risk to which each subject might be exposed are more responsible for the increased absolute risk of major CV events than that derived from high-risk levels involving only limited proportions of patients.

This evidence is confirmed by the fact that the vast majority of CV events occur in low- or intermediate-risk categories, whereas only a minor proportion of events occurs in individuals at high or very high risk (14,15). For these reasons, prevention strategies should ideally be applied to the entire population, including young adults, throughout all risk categories, and the intensity of the therapeutic approach should take into account not only the absolute level of single CV risk factors but also the potential impact of the size of the abnormality of concomitant risk factors, particularly BP and LDL-c levels.

With regard to dyslipidaemias, specific recommendations about when to start pharmacological therapies and how many times the assessment of lipid profile should be repeated are currently lacking. According to European guidelines, screening should be carried out in men aged >40 years and women aged >50 years or in post menopause, whereas it is not indicated in younger people without other additional risk factors. In addition, patients with diabetes, peripheral artery disease, hypertension or with family history of premature CV events should undergo lipid evaluation at the time of the diagnosis, independently from age (16). Indications for starting and/or maintaining lipid-lowering therapies are discussed below.

### LIPID-LOWERING THERAPIES AND HYPERTENSION

Since there is clear evidence that dyslipidaemia and hypertension have a synergistic impact on the genesis and progression of atherosclerotic disease, with relevant clinical consequences on the risk of developing major CV events, such as coronary artery disease, stroke, heart failure and CV mortality, it is necessary to focus on both primary and secondary prevention of these conditions by adopting early pharmacological interventions and long-term clinical management in order to the recommended target LDL-c and BP levels.

Recent guidelines have recommended therapeutic thresholds of LDL-c lower than those previously set, mostly when multiple CV and metabolic risk factors coexist, and even in the low- to intermediate-risk patients. In this view, the NCEP ATP guidelines support the benefits of reducing cholesterol in the presence of concomitant risk factors, even when plasma levels of LDL-c are not elevated, and suggest considering the start of lipid-lowering therapy in all hypertensive patients, independently from their lipid profile (17).

Among different components of the lipid profile, the reduction of LDL-c plasma concentrations represents the most important therapeutic target due to its pathological role in increasing risk of coronary and cerebrovascular

events. Indeed, therapeutic strategies aimed at reducing levels of triglycerides or increasing levels of HDL-c have displayed less consistent proofs of providing benefits in reducing the incidence rate of major CV events (18,19).

The suggested therapeutic targets of LDL-c derive from the results of several randomized clinical trials, and depend mostly on individual CV risk profile. It should be noted that the absolute benefit of lowering LDL-c depends on the absolute individual risk rather than the baseline plasma LDL-c levels. Thus, guidelines currently focus not only on LDL-c plasma concentrations, but also on baseline estimated CV risk profile.

In patients at very high CV risk, a reduction of LDL-c levels below 70 mg/dL or at least 50% from baseline value should be obtained. In those individuals at high CV risk, the therapeutic target is LDL-c <100 mg/dL, whereas in those with moderate CV risk the goal of <115 mg/dL can be achieved (13).

These recommendations are supported by the recent results of the Heart Outcomes Prevention Evaluation (HOPE-3) trial, that demonstrated significantly beneficial effects of rosuvastatin 10 mg compared to placebo in reducing major CV events (24%), also in individuals at moderate risk with at least one risk factor in the setting of primary prevention (20).

The United States Preventive Services Task Force (USPSTF) recommend starting lipid-lowering therapies, especially with low- to moderate-intensity statins, in adults aged between 40–75 years with the following additional CV risk factors: smoking, hypertension, dyslipidaemia, diabetes or at least a 10% 10-year CV risk. If the estimated 10-year risk is between 7.5% and 10%, starting pharmacological therapy is not mandatory and physicians should take into account the patient's preferences and attitudes, and may give high priority to lifestyle recommendations (21).

The ACC/AHA Guidelines on the Treatment of Blood Cholesterol, published in 2013, emphasize that high LDL-c levels represent a risk factor for vascular disease even in young adults. In subjects aged 40–75 years, without previous history of CV disease or diabetes, with LDL-c concentrations 70–189 mg/dL, the initiation of a statin therapy is suggested independently from sex and race since the benefits in terms of relative risk reductions of major events in primary prevention do not differ between men or women or between different ethnicities. Intensity of statin treatment should be adapted to the estimated 10-year CV risk.

Because the relative risk reduction does not differ at different LDL-c levels between 70–189 mg/dL, according to several studies, the absolute benefit of statin therapy in primary prevention depends on the global 10-year estimated risk (22).

As observed in the aforementioned USPSTF recommendations (23), a shared decision between patients and physicians on starting statin therapy in subjects with a CV risk of 7.5% or 5% to <7.5% is suggested. Physicians should take into account potential benefits, adverse events and individual preferences.

Additional factors should be also considered when undertaking treatment decision. Among these, one should consider family history of premature onset of CV disease <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative, ankle-brachial index <0.9 and also elevated lifetime risk of major events, considering that the 10-year horizon might be not sufficient in some circumstances. In addition, the same guidelines recommend

consideration of not only hard endpoints of coronary artery disease, including fatal and nonfatal myocardial infarction, but also stable and unstable angina and cerebrovascular disease in the assessment of the 10-year risk.

Several studies have demonstrated a continuous positive association between LDL-c concentrations and the incidence of vascular disease, but a threshold below which the risk of CV events is almost eliminated has not been yet identified, and the former thresholds have been challenged by recent studies (23).

## CLINICAL SURVEYS ON STATIN THERAPY

There are also many observational studies and clinical surveys reporting favourable effects of statin therapy on BP reduction and control. For example, the Brisighella Heart Study evaluated the effects of different strategies of lipid lowering on BP, comparing diet, cholestyramine, gemfibrozil and simvastatin, demonstrating the greatest results in the group treated with simvastatin (24).

Similar results have been obtained by Borghi and co-workers, who demonstrated that the use of statins, beyond antihypertensive drugs, may improve BP control. In this study, the administration of statins in combination with a calcium channel blocker significantly reduced BP more than the calcium channel blocker alone (25).

Tocci et al. have recently investigated the potential effects of statins on nighttime ambulatory systolic and diastolic BP and on home, clinic, ambulatory daytime and 24-hour systolic and diastolic BP in a cohort of 5634 patients. Among individuals who did or did not receive statin treatment, there were significant differences in terms of 24-hour (129.7 vs. 130.9 mmHg, respectively) and daytime systolic BP (133.0 vs. 134.5 mmHg), and in terms of home (80.7 vs. 84.5 mmHg), clinic (86.5 vs. 91.7 mmHg), 24-hour (75.0 vs. 79.9 mmHg), daytime (78.0 vs. 83.3 mmHg) and nighttime (67.3 vs. 70.9 mmHg) diastolic blood pressure. These effects on BP profile are consistent not only in hypertensive patients, but also in normotensive patients, regardless of the classes and the numbers of antihypertensive drug administered in free- or fixed-dose combinations (26).

These results may explain and further support the evidence of a synergistic effect of statins and BP-lowering therapies in reducing the development and progression of atherosclerosis and the incidence of CV and cerebrovascular events. In fact, these findings corroborate previous large epidemiological observations, such as those obtained in the Asian-Pacific Study (27), where the negative synergistic effect of BP and cholesterol on myocardial infarction and stroke was clearly demonstrated, and it was hypothesized that a combined reduction of 10 mmHg systolic BP and 1 mmol cholesterol doubled the CV benefits.

## CLINICAL TRIALS ON STATIN THERAPY

Numerous randomized controlled clinical trials have demonstrated the efficacy of statins in reducing CV morbidity and mortality, both in primary and secondary prevention and independently from age and sex. It should be noted that, regrettably, very often data and trends of BP during a trial are not reported, and a greater attention to the collection of these data should be encouraged.



The Cholesterol Treatment Trialists' (CTT) Collaboration has analysed data from 27 trials involving 170,000 individuals treated with more or less intensive regimens. This analysis demonstrated that a reduction of 40 mg/dL of LDL-c is able to produce 10%, 20%, 23% and 17% reductions of all-cause mortality, CV mortality, major coronary events and ICH, respectively, with more intensive statin regimens being even more efficacious (28). The observed benefits achieved statistical significance even after the first year of therapy and persisted for many years even after treatment discontinuation. However, the benefits in terms of CV prevention became greater during each year in those patients who remained on treatment. In this meta-analysis, statin therapy significantly reduced the risk of major events even in individuals with 5-year risk lower than 10% and without diabetes, chronic kidney disease and history of previous vascular disease.

A meta-analysis of eight controlled, lipid-lowering trials involving 18,000 patients has shown a reduction of systolic BP between 1.3 and 6 mmHg in subjects who received lipid-lowering treatment (29).

In non-placebo-controlled trials, both pravastatin and atorvastatin (30,31) produced a mean reduction of 8 mmHg for systolic BP and a mean reduction of 5 mmHg for diastolic BP levels. The obtained BP reduction was not related to the mean decrease of cholesterol levels, thus confirming the hypothesis that the BP-lowering effect of statins is independent from their ability to lower LDL-c levels.

Another meta-analysis has shown that statin treatment reduced systolic BP by 1.9 mmHg and diastolic BP by 0.9 mmHg, with a greater effect in patients with higher baseline BP. Results obtained were even more marked in diabetic patients with hypercholesterolemia, with a reduction of 3.7 and 0.8 mmHg for systolic and diastolic BP, respectively. These findings were independent of age, length of the trial, baseline plasmatic concentrations of total and LDL cholesterol and antihypertensive medications (32).

A sub-analysis of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) showed that after a 2.5-year follow-up BP was significantly lower in patients treated with atorvastatin than in those who received placebo (33). Similar data have been obtained by the San Diego Statin Study, in which treatment with simvastatin or pravastatin produced a significantly greater reduction of BP compared to placebo, with a maximum difference of 2.8/2.7 mmHg (34).

In the Steno-2 study, intensive intervention on multiple risk factors (identified targets: levels of glycated haemoglobin <6.5%, of total cholesterol <175 mg/dL and of triglycerides <150 mg/dL, BP <130/80 mmHg) had sustained beneficial effects on the rate of vascular complications and of CV and all-cause mortality (35).

The ENCORE II study enrolled 226 patients with a left coronary artery stenosis with the aim to evaluate the potential synergism of lipid and BP-lowering therapies. The study demonstrated that the addition of nifedipine to statin treatment significantly improved coronary endothelial function and inflammatory markers (36).

In the ASCOT Lipid-Lowering Arm (ASCOT-LLA) trial, 10,305 patients with hypertension and average total cholesterol levels of 252 mg/dL were randomly assigned to atorvastatin 10 mg daily or placebo. In patients treated with atorvastatin, 36% fewer fatal coronary events and nonfatal myocardial infarction occurred compared to the placebo group. It must be emphasized that these results

have been obtained in a setting of satisfactory BP control (mean values 138/80 mmHg) in both groups, indicating that the effects of statins are additive to those of the antihypertensive regimen (37).

The benefits of simultaneous modifications of risk factors are particularly evident in subjects with impaired glucose metabolism. The co-administration of amlodipine and atorvastatin produced greater reductions of both BP and inflammatory markers compared to those obtained with each therapy administered separately. Indeed, the amlodipine-atorvastatin combination produced a greater decrease of 22.5 mmHg for systolic BP and 17.7 mmHg for diastolic BP compared to 17.1 and 14.3 mmHg obtained with amlodipine monotherapy. The combination therapy also produced greater reductions of tumor necrosis factor (TNF) levels (2.59 pg/mL vs. 0.57 pg/mL in the amlodipine group) and of homeostasis model assessment (HOMA-IR) (2.86 vs. 0.70 in the amlodipine group). HOMA-IR changes significantly correlated with TNF- $\alpha$  changes ( $r = 0.38$ ) during combination but not during amlodipine monotherapy (38). Subsequent studies confirmed that the combination of atorvastatin to amlodipine therapy has an additive role in increasing arterial compliance and reducing arterial stiffness and BP (39).

The synergistic beneficial role of antihypertensive and statin therapies in reducing CV risk is particularly relevant in secondary prevention, such as in patients with a history of myocardial infarction.

A sub-study from the IDEAL trial has investigated the effects of BP and LDL-c visit-to-visit variability on a composite endpoint of death from CV causes, nonfatal myocardial infarction, revascularization or angina. The composite endpoint was characterized by any CV event (any coronary event or cerebrovascular event, peripheral vascular disease, heart failure) and individual endpoints of myocardial infarction, stroke, death and CV death evaluated separately (40). The increase of about 11 mg/dL of LDL-c levels was associated with a significantly augmented incidence of any coronary event (7%), any CV event (8%), myocardial infarction (11%) and death (19%). For each increase in systolic BP variability of 7.2 mmHg, an increased risk of any coronary event (15%), any CV event (16%), myocardial infarction (28%), stroke (33%), death from any cause (28%) and from CV cause (19%) was detected.

Both LDL-c and BP variabilities were independent of each other in predicting any coronary event. However, the group with high variability for both these risk factors had a significant increase in any coronary event (HR 1.48), any CV event (HR 1.43) and myocardial infarction (HR 1.87) compared to subjects with low variability of both LDL-c and blood pressure. Variability in systolic BP strongly predicted the risk of stroke compared to the variability in LDL-c.

On the basis of the results of these trials, the American College of Cardiology/American Heart Association 2013 Blood Cholesterol Guideline has stratified statin regimens into low- to high-intensity statins: (a) low-intensity statins, such as simvastatin 10 mg daily, are able to produce a <30% reduction of cholesterol levels; (b) moderate-intensity statins, such as simvastatin 20–40 mg, atorvastatin 10–20 mg or rosuvastatin 5–10 mg daily, can reduce cholesterol concentration by a percentage between 30% and <50%; (c) high-intensity statins, such as atorvastatin 40–80 mg or rosuvastatin 20–40 mg daily cause a >50% decrease in plasmatic cholesterol levels (23).

When high-intensity statin treatment cannot be undertaken, the combination with ezetimibe (41) or alternative cholesterol-lowering strategies, for instance protein convertase subtilisin-kexin 9 (PCSK-9) inhibitors (42,43), can be considered, especially for high levels of cholesterol or very high-risk patients who need to achieve very ambitious therapeutic targets.

## CONCLUSIONS

Several conclusions can be drawn from what we have learned over the last 30 years from randomized controlled clinical trials as well as from epidemiological studies and clinical surveys. First, the concomitant presence of dyslipidaemia and hypertension is very frequent in the general population. There is considerable evidence that hypertension, dyslipidaemia and other risk factors synergistically raise CV risk and increase exposure to CV accidents. Individuals with both hypertension and dyslipidaemia have a significantly greater absolute risk for myocardial infarction and stroke compared to subjects without either of these risk factors, or those with at least one risk factor. Accordingly, it is currently demonstrated that a significant reduction of CV and cerebrovascular events can be obtained only achieving the recommended targets of both risk factors. Further studies will better define the recommended targets of BP and LDL-c in patients at different levels of risk and define whom to treat, how much to treat and when to start both screening tests and therapeutic interventions.

## REFERENCES

- Wilson PW, Kannel WB, Silbershatz H, D'Agostino RB. Clustering of metabolic factors and coronary heart disease. *Arch Intern Med* 1999; 159: 1104–1109.
- Mancia G et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; 34: 2159–2219.
- Mason RP, Jacob RF. Membrane microdomains and vascular biology: Emerging role in atherogenesis. *Circulation* 2003; 107: 2270–2273.
- Cardillo C, Kilcoyne CM, Cannon RO 3rd, Panza JA. Increased activity of endogenous endothelin in patients with hypercholesterolemia. *J Am Coll Cardiol* 2000; 36: 1483–1488.
- Daugherty A et al. Hypercholesterolemia stimulates angiotensin peptide synthesis and contributes to atherosclerosis through the AT1A receptor. *Circulation* 2004; 110: 3849–3857.
- Shen BJ et al. Are metabolic risk factors one unified syndrome? Modeling the structure of the metabolic syndrome X. *Am J Epidemiol* 2003; 157: 701–711.
- Leyva F et al. Factors of the metabolic syndrome: Baseline interrelationships in the first follow-up cohort of the HDDRISC Study (HDDRISC-1). Heart Disease and Diabetes Risk Indicators in a Screened Cohort. *Arterioscler Thromb Vasc Biol* 1998; 18: 208–214.
- Laaksonen DE et al. Dyslipidaemia as a predictor of hypertension in middle-aged men. *Eur Heart J* 2008; 29: 2561–2568.
- Hunt SC, Stephenson SH, Hopkins PN, Williams RR. Predictors of an increased risk of future hypertension in Utah. A screening analysis. *Hypertension* 1991; 17: 969–976.
- Sesso HD et al. A prospective study of plasma lipid levels and hypertension in women. *Arch Intern Med* 2005; 165: 2420–2427.
- Syvanne M, Taskinen MR. Lipids and lipoproteins as coronary risk factors in non-insulin-dependent diabetes mellitus. *Lancet* 1997; 350(Suppl. 1): S120–S123.
- Piepoli MF et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016; 37(29): 2315–2381.
- Conroy RM et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: The SCORE project. *Eur Heart J* 2003; 24: 987–1003.
- Giampaoli S et al. La carta Italiana del rischio cardiovascolare globale. *It Heart J Suppl* 2004; 5: 177–185.
- Giampaoli S. CUORE: A sustainable cardiovascular disease prevention strategy. *Eur J Cardiovasc Prev Rehabil* 2007; 14: 161–162.
- Chapman MJ et al. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: Evidence and guidance for management. *Eur Heart J* 2011; 32: 1345–1361.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001; 285: 2486–2497.
- Fruchart JC, Sacks F, Hermans MP. The residual risk reduction initiative: A call to action to reduce residual vascular risk in patients with dyslipidemia. *Am J Cardiol* 2008; 102(10 Suppl): 1K–34K.
- Voight BF et al. Plasma HDL cholesterol and risk of myocardial infarction: A mendelian randomisation study. *Lancet* 2012; 380: 572–580.
- Lonn EM et al. HOPE-3 Investigators. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease (HOPE-3). *N Engl J Med* 2016; 374(21): 2009–2020.
- US Preventive Services Task Force et al. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA* 2016; 316(19): 1997–2007.
- Stone NJ et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63(25).
- Sabatine MS et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017; 376: 1713–1722.
- Borghi C, Dormi A, Veronesi M, Sangiorgi Z, Gaddi A. Association between different lipid-lowering treatment strategies and blood pressure control in the Brisighella Heart Study. *Am Heart J* 2004; 148: 285–292.
- Borghi C et al. Use of statins and blood pressure control in treated hypertensive patients with hypercholesterolemia. *J Cardiovasc Pharmacol* 2000; 35: 549–555.
- Tocci G et al. Favourable impact of statin use on diastolic blood pressure levels: Analysis of a large database of 24-hour ambulatory blood pressure monitoring. *J Hypertens* 2017; 35: 2086–2094.
- Lawes CM et al. Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular disease in the Asia Pacific region. *J Hypertens* 2003 April; 21(4): 707–16.
- Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: Meta-analysis of individual data from 27 randomised trials. *Lancet* 2012; 380: 581–590.
- Goode GK, Miller JP, Heagerty AM. Hyperlipidaemia, hypertension, and coronary heart disease. *Lancet* 1995; 345: 362–364.
- Glorioso N et al. Effect of the HMG-CoA reductase inhibitors on blood pressure in patients with essential hypertension and primary hypercholesterolemia. *Hypertension* 1999; 34: 1281–1286.
- Bandinelli S et al. Hypotensive effects of statins: Preliminary data with atorvastatin. *J Hypertens* 1999; 17(Suppl 3): S59–S60.
- Strazzullo P et al. Do statins reduce blood pressure? A meta-analysis of randomized, controlled trials 10.1161/01.HYP.0000259737.43916.42. *Hypertension* 2007; 49: 792–798.
- Dahlof B, Poulter N, Sever PS. Do statins lower blood pressure? Evidence from the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid-Lowering Arm (ASCOT-LLA) (abstract). *Circulation* 2004; 110: 402.
- Golomb BA, Ritchie JB, Criqui MH, Dimsdale JE. Statins lower blood pressure: Results from the UCSD Statin Study (abstract). *Circulation* 2004; 110: 402.
- Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008; 358: 580–591.
- Lüscher T. Long-Term Effect of Nifedipine on Vasomotion and Vessel Morphology in Patients with Coronary Artery Disease: An Intravascular Ultrasound-Assisted Evaluation. Presentation at the European Society of Cardiology, Munich; 2004.

37. Sever PS et al. for the ASCOT Investigators: Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): A multicentre randomised controlled trial. *Lancet* 2003; 361: 1149–1158.
38. Fogari R et al. Effects of amlodipine-atorvastatin combination on inflammation markers and insulin sensitivity in normocholesterolemic obese hypertensive patients. *Eur J Clin Pharmacol* 2006; 62: 817–822.
39. Leibovitz E, Beniashvili M, Zimlichman R. Treatment with amlodipine and atorvastatin have additive effect in improvement of arterial compliance in hypertensive hyperlipidemic patients. *Am J Hypertens* 2003; 16: 715–718.
40. Bangalore S et al. Relation of variability of low-density lipoprotein cholesterol and blood pressure to events in patients with previous myocardial infarction from the IDEAL trial. *Am J Cardiol* 2017; 119: 379–387.
41. Cannon CP et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015; 372: 2387–2397.
42. Robinson JG et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015; 372: 1489–1499.
43. Sabatine M et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015; 372: 1500–1509.

# Section IV

## Blood Pressure Measurements

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# OLD AND NEW OFFICE BLOOD PRESSURE MEASUREMENT APPROACHES

# 21

*Michael Bursztyn and Iddo Z. Ben-Dov*

## INTRODUCTION

The indirect sphygmomanometry technique for measurement of systolic blood pressure (SBP) developed by Riva-Rocci (1) at the end of the nineteenth century, and that of systolic and diastolic blood pressure (DBP) invented by Korotkoff (2) at the beginning of the twentieth century, have yielded major achievements: BP measurement was rapidly adopted as a standard part of physical examination, and it served to produce an enormous, consistent prognostic database from observational studies and randomized controlled studies, establishing the role of hypertension as a major modifiable cardiovascular risk factor. This has led to worldwide assimilation of interventions to routine clinical practice, with enormous health benefits.

Nevertheless, office BP (OBP) measurement is not a trivial procedure, as many believe. From the outset, Riva-Rocci was aware of many of the pitfalls we acknowledge to this date (1):

...Although it is not the only factor, the simple application of the instrument can cause a temporary rise in blood pressure. It is therefore necessary to take not just one reading but several in succession.

The last statement refers to a phenomenon now loosely called the 'white-coat effect', 'white-coat hypertension' or 'isolated office hypertension', made evident first with intra-arterial ambulatory blood pressure monitoring (ABPM) (3), and confirmed by automated noninvasive measurements, both ABPM and home blood pressure (HBP) monitoring. It is clear that repeated OBP measurements are less prone to these transient elevations (4) but physicians devoted to such undertaking are the minority, and it may not be feasible in all clinical settings.

Although the precise nature of the white-coat effect is not clear, it is assumed to be caused by some form of anxiety, a specific 'state anxiety' according to one study (5), reflecting fluctuations that occur in the medical environment, most likely mediated by an adrenergic reaction (6) even when BP is self-measured in the clinic (7). There is a gradient from the highest pressure and adrenergic

response to a physician's measurement, through lesser degrees when a nurse measures BP (6). There is uncertainty about characteristics of patients with this phenotype, some stating higher age, female gender (8), and the presence of metabolic abnormalities (9). Consistently though, the higher the clinic pressure is, the higher is the white-coat effect (10,11). White-coat hypertension prevalence ranges from 10–40% of examinees, depending to a great extent on the age and nature of the studied population (referred or general population), level of the ambulatory BP (8), and on the reference value; daytime (as in most studies), nighttime (as in some), 24-hour, or as recently suggested, a composite of daytime, nighttime and 24-hour period (12). White-coat effect also depends on the OBP technique, number of measurements, and the number of measurement occasions (6).

However, since the advent of widespread ABPM and HBPM, a mirror phenotype has become evident, frequently called 'masked hypertension', or 'isolated office normotension', where OBP is found normal in the presence of elevated out-of-office BP (10,13,14). Subjects with masked hypertension have target-organ damage (12) and adverse outcomes similar to those with sustained hypertension. They were in some studies found to be predominantly male (6,13), younger (6), employed (14,15) and, according to a recent estimation, may comprise about 12% of the general adult population (16).

One of the features in common to white-coat and masked hypertension is that they are more common in patients with clinic BP close to the cutoff (from above, or below, respectively) (17). It is not surprising that patients with either phenotype were found to have increased BP variability (18), which increases the risk of misclassification.

Realization that target-organ damage and outcome track better with out-of-office BP is one of the reasons for introduction of new OBP measurement techniques (see below), and motivated some authorities, notably the British NICE, to favour out-of-office diagnosis of hypertension (19).

However, the bad reputation of OBP measurements has to do with the fact that they are consistently performed not according to recommendations. Indeed, loose terms such as 'casual' OBP or 'manual' OBP are used to suggest the questionable quality of the measurement. Interestingly,

Riva-Rocci was aware of many of these deficiencies, from the inception of systematic BP measurement (1):

... It is enough to speak to the patient, invite him to read, or look at him suddenly, or perhaps it will take a sudden noise, a carriage going past in the street, a shout of a loud but distant noise to make the blood pressure rise, and not necessarily to the same extent in all cases.

Sources of variability include examiner factors, examinee factors (20), intrinsic variability and seasonal variability (21) as well as other recognized and as-yet unrecognized factors.

As noninvasive arterial BP measurement is indirect; namely, pressure is measured within the bladder of the manometer, presence of muscle tone in the arm may have a substantial effect. Hence the importance of arm support at the level of the heart to avoid not only gravitational but also other effects related to arm position (22). Comfortable seating with the back supported, feet on the ground, not crossed (23) and not hanging off an examination table, is also required for accurate readings.

Some sources of variability, when acknowledged (Table 21.1), are correctable. A common mistake is using a cuff too small for the arm, more frequent now due to the obesity epidemic. If the bladder is too short for the arm's circumference, a greater pressure needs to be generated within it to occlude the artery, compared to the distending pressure, thus yielding falsely elevated readings. When such mistakes are recognized, they are correctable. However, all too frequently this does not happen and the mistake may be reiterated, and in such cases repeated measurements will not improve accuracy. Occasionally measurement problems may be related to the examinee, who enters the examination room with a distended urinary bladder, in order not to miss his/her turn in queue. Other factors that may elevate OBP inadvertently are speaking during OBP measurement, sitting with legs crossed (23),

and people entering unexpectedly into the examination room. Environmental factors such as cold temperatures (24), wintertime and short light hours (25) may also be associated with higher OBP.

Initially, OBP should be determined in both arms, as there may be a difference between arms in OBP (26), which when consistent and sizeable ( $>10$  mmHg) carries prognostic significance and points to more extensive vascular disease of some cause. However, it is a tricky finding, as instruments for simultaneous two-arm measurements are expensive and often unavailable (when available, they can be useful also for the purpose of evaluating the oscillometric ankle-brachial index (27)). Moreover, many patients may falsely attribute variation between successive measurements to inter-arm differences (28); therefore, repeated examination of OBP in alternating arms may prevent misclassification. If consistent, it is important to subsequently measure OBP in the arm with the higher reading.

Older patients, those with diabetes mellitus, and those treated with medications, particularly  $\alpha$ -blockers, should be examined for orthostatic hypotension (a reduction of  $\geq 20$  mmHg systolic or  $\geq 10$  mmHg diastolic) after 1 and 3 minutes of standing, because orthostatic hypotension is common, symptomatic at times, antedates falls and injuries, and has prognostic significance (29). Recently it was suggested that orthostatic hypertension, a BP rise of similar magnitude, is associated with adverse outcome (30), though this is not a consistent finding (31).

OBP measurements in the presence of atrial fibrillation (AF) are prone to error due to beat-to-beat variability. Guidelines (although not most recent) recommend repeated auscultatory clinic measurements in patients with AF (32). Most validation studies of automated BP monitors excluded subjects with irregular heart rhythm (33). Nonetheless, a recent small meta-analysis suggests that the oscillometric method is accurate for SBP, and possibly overestimates DBP (mean differences  $+0.5/+2.5$  mmHg). Correlation coefficients with the reference noninvasive

**Table 21.1** Factors affecting the accuracy of office BP measurements

| Increase BP                 | Decrease BP                 | No effect on BP              |
|-----------------------------|-----------------------------|------------------------------|
| <i>Examinee</i>             | <i>Examinee</i>             | <i>Examinee</i>              |
| Pseudohypertension          | Recent meal                 | Chronic caffeine ingestion   |
| White-coat hypertension     | Missed auscultatory gap     | Cuff self-inflation          |
| Paretic arm (due to stroke) | High stroke volume          | <i>Examinee and examiner</i> |
| Pain, anxiety               | <i>Setting equipment</i>    | Discordant gender or race    |
| Acute smoking               | Noisy environment           | <i>Examination</i>           |
| Acute caffeine              | Faulty aneroid device       | Thin shirt sleeve under cuff |
| Acute ethanol ingestion     | Low mercury level           | Bell vs. diaphragm           |
| Distended bladder           | Leaky bulb                  |                              |
| Talking                     | <i>Examiner</i>             |                              |
| <i>Setting, equipment</i>   | Rounding to next lower      |                              |
| Cold environment            | 5–10 mmHg, expectation bias |                              |
| Leaky bulb valve            | Impaired hearing            |                              |
| <i>Examination</i>          | Stethoscope under cuff      |                              |
| Cuff too narrow             | <i>Examination</i>          |                              |
| Arm below heart level       | Resting too long            |                              |
| Too short rest period       | Arm above heart level       |                              |
| Arm, back unsupported       | Too rapid deflation         |                              |
| Using phase IV (adult)      | Excess bell pressure        |                              |

Source: Modified from Kallioinen N et al. *J Hypertens* 2017; 35(3): 421–441 (20).

method were  $r = 0.89$  for SBP and  $r = 0.76$  for DBP. Agreement of oscillometry with invasive BP measurements in patients with AF was moderate in one study (34). In another, when three oscillometric measurements were averaged and compared with intra-arterial readings, the biases of SBP and DBP did not significantly differ in the presence or absence of AF (35). Currently, oscillometric devices are deemed acceptable for home and ambulatory monitoring of patients with AF, but not recommended for clinic setting (33).

Another noteworthy aspect is the opportunity to detect asymptomatic AF during clinic BP measurement. Indeed, a NICE Medical Technology Guidance Committee recommended AF screening with a particular oscillometric device (36), and real-life assessment offered some support for clinical utility (37).

Devices also play a role in OBP measurement precision and accuracy. The auscultatory method is plagued with issues such as examiner's hearing, prejudice and number rounding. The latter bias was addressed with random zero sphygmomanometers, eventually found to be inaccurate (38). Given the phase-out of mercury sphygmomanometers (which need verification of the zero Hg level) because of toxicity-related bans (39), we are left with aneroid sphygmomanometers requiring frequent calibration due to time- and use-dependent decay of spring elastics (40). All too frequently this recalibration is not performed. Oscillometric sphygmomanometers, commonplace these days, are certainly devoid of prejudice, digit preference and auscultation capacity, but have other setbacks. These instruments are based on detection of cuff oscillations when pressure approaches SBP (in deflating oscillometry) and recognition of maximal oscillations which indicate mean arterial pressure. DBP, however, is calculated by

way of manufacturers' proprietary algorithms. Therefore, all oscillatory instruments need unbiased validation, also in specific populations (e.g. children, severe obesity, pregnant women (41)). Given the plethora of producers, models of even the same brand, and physical differences, not to mention a surfeit of validation methods and authorities, it should not be surprising that not all models have been validated successfully and many have not even attempted validation (42).

Despite the deficiencies of OBP measurement, it has served the vast majority of observational and randomized controlled trials. Moreover, even in the era of HBPM and ABPM, OBP retains prognostic significance (9), hence is here to stay, and we are destined to carry it out optimally. Instructions for such conduct, based on American Heart Association (43), and European Society of Hypertension recommendations (44), are compiled in Table 21.2 (and videotaped by Williams et al. (45)).

Recently, a model that includes three OBP measurements and clinical characteristics was developed that predicts white-coat and masking effects with reasonable sensitivity and specificity. This may help triage patients' referral for out-of-office BP monitoring (46).

## AUTOMATED OFFICE BLOOD PRESSURE

The recognition that white-coat hypertension is common and may be related to the presence of the physician (or nurse) (3,5,6), together with technical advances which allow multiple fully automated in-clinic measurements as they do in ABPM, brought about a new concept for OBP measurement: automated office blood pressure (AOBP).

**Table 21.2** Office BP measurement

| Feature                    | Recommendations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Patient preparation</i> | <ol style="list-style-type: none"> <li>1. Have the patient relax, sitting in a chair, feet on floor, back supported, for &gt;5 min.</li> <li>2. The patient should avoid caffeine, exercise and smoking for at least 30 min before measurement.</li> <li>3. Ensure patient has emptied his/her bladder.</li> <li>4. Neither the patient nor the observer should talk during the rest period or during the measurement.</li> <li>5. Remove all clothing covering the location of cuff placement.</li> <li>6. Avoid measuring while the patient is sitting or lying on an examining table.</li> </ol>        |
| <i>Device preparation</i>  | <ol style="list-style-type: none"> <li>1. Use a device that has been validated and ensure that the device is calibrated periodically.</li> <li>2. Support the patient's arm (e.g. resting on a desk).</li> <li>3. Position the middle of the cuff on the patient's upper arm at the level of the right atrium (the midpoint of the sternum).</li> <li>4. Use the correct cuff size, such that the bladder encircles 80% of the arm, and note if a larger- or smaller-than-normal cuff size is used.</li> <li>5. Either the stethoscope diaphragm or bell may be used for auscultatory readings.</li> </ol> |
| <i>Technique</i>           | <ol style="list-style-type: none"> <li>1. At the first visit record BP in both arms. Use the arm that gives the higher reading for subsequent readings.</li> <li>2. Separate repeated measurements by 1–2 min.</li> <li>3. For auscultatory determinations, use a palpated estimate of radial pulse obliteration pressure to estimate SBP. Inflate the cuff 20–30 mmHg above this level for the auscultatory determination.</li> <li>4. For auscultatory readings, deflate the cuff pressure 2–3 mmHg/sec, and listen for Korotkoff sounds.</li> </ol>                                                     |
| <i>Documentation</i>       | <ol style="list-style-type: none"> <li>1. Record SBP and DBP. If using the auscultatory technique, record SBP and DBP as onset of the first Korotkoff sound and disappearance of all Korotkoff sounds, respectively, using the nearest even number.</li> <li>2. Note the time of most recent BP medication taken before measurements.</li> <li>3. Use an average of <math>\geq 2</math> readings obtained on <math>\geq 2</math> occasions to estimate the individual's level of BP.</li> <li>4. Provide patients their BP readings both verbally and in writing.</li> </ol>                               |

Source: Modified from Whelton PK et al. 2017 *Hypertension* 2017; 71(6): 1269–1324 (43).

With this procedure, multiple BP readings are obtained with the patient resting undisturbed in a quiet place without medical staff present (47). It was found that physicians measure OBP differently in their clinical practice compared to research settings, in which they apply accepted methods as described above (48); hence the average OBP is significantly higher in clinical practice compared to research (46), which is in turn higher than ABPM. AOBP achieves an average quite similar to that of ABPM (48). That AOBP is lower than mercury sphygmomanometry was confirmed in large population surveys (48,49), in primary care (50), in hypertension clinics (51) and in community pharmacies (52). AOBP also correlated better than OBP with left ventricular mass (51), and urine albumin:creatinine ratio (49).

AOBP deals well with the white-coat issue (53) by removing the effect of attending medical personnel and reducing the alerting response (51). Within the context of two relatively large population-based samples on two continents, prevalence of masked hypertension by way of AOBP was found to be around 10% (49,54), similar to what was found when defined by ABPM (12–15). Therefore, if OBP misclassification is improved with AOBP, the tighter associations of AOBP with hypertensive target-organ damage (49,50) should not be surprising.

On this background, AOBP was chosen to be used for the first time in the Systolic Blood Pressure Intervention Trial (SPRINT) (55), which randomized 9631 high-risk patients to a target of either <140 mmHg or <120 mmHg systolic BP. The trial demonstrated superiority of the lower AOBP target (56). This brought about controversy, centred on the differences between AOBP and methods used in previous studies (57). The generalizability of the results was questioned. This is a valid point and educated extrapolations may be required for proper comparisons (58). Nevertheless, OBP taken in both randomized controlled and observational trials used research-level OBP methodology rarely practiced in the clinical world, sustaining similar levels of doubt regarding generalizability.

Given this controversy, or perhaps regardless the controversy, observational studies on two continents, applying AOBP monitoring, surveyed the validity of the SPRINT methodology and results and found that AOBP was not inferior to traditional OBP in predicting cardiovascular events (59), and affirming that in a real-world setting, AOBP category of 120–129 mmHg systolic associated with a hazards ratio of 1.33 (95% confidence interval, 1.02–1.725) compared to lower values (60).

On the basis of these and additional arguments, Hypertension Canada's 2017 Guidelines call to adopt AOBP as the preferred measure of BP in the office (61). If widely adopted, a scenario not immediately likely in most clinical practices, such recommendations may prominently transform hypertension management.

## REFERENCES

1. Riva-Rocchi S, Zanchetti A, Mancia G. A new sphygmomanometer. Sphygmomanometric technique. *J Hypertens* 1996; 14(1): 1–12.
2. Segall HN. How Korotkoff, the surgeon, discovered the auscultatory method of measuring arterial pressure. *Ann Intern Med* 1975; 83(4): 561–562.
3. Mancia G, Bertinieri G, Grassi G et al. Effects of blood-pressure measurement by the doctor on patient's blood pressure and heart rate. *Lancet* 1983; 2(8352): 695–698.
4. Pearce KA, Grimm RH, Jr., Rao S et al. Population-derived comparisons of ambulatory and office blood pressures. Implications

- for the determination of usual blood pressure and the concept of white coat hypertension. *Arch Intern Med* 1992; 152(4): 750–756.
5. Ogedegbe G, Pickering TG, Clemow L et al. The misdiagnosis of hypertension: The role of patient anxiety. *Arch Intern Med* 2008; 168(22): 2459–2465.
6. Grassi G, Seravalle G, Buzzi S et al. Muscle and skin sympathetic nerve traffic during physician and nurse blood pressure measurement. *J Hypertens* 2013; 31(6): 1131–1135.
7. Stergiou GS, Efstathiou SP, Alamará CV et al. Home or self blood pressure measurement? What is the correct term? *J Hypertens* 2003; 21(12): 2259–2264.
8. Conen D, Aeschbacher S, Thijs L et al. Age-specific differences between conventional and ambulatory daytime blood pressure values. *Hypertension* 2014; 64(5): 1073–1079.
9. Mancia G, Facchetti R, Bombelli M et al. Long-term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure. *Hypertension* 2006; 47(5): 846–853.
10. Banegas JR, Ruilope LM, de la Sierra A et al. Clinic versus daytime ambulatory blood pressure difference in hypertensive patients: The impact of age and clinic blood pressure. *Hypertension* 2017; 69(2): 211–219.
11. Ben-Dov IZ, Ben-Arie L, Mekler J, Bursztyn M. In clinical practice, masked hypertension is as common as isolated clinic hypertension: Predominance of younger men. *Am J Hypertens* 2005; 18(5 Pt 1): 589–593.
12. de la Sierra A, Vinyoles E, Banegas JR et al. Prevalence and clinical characteristics of white-coat hypertension based on different definition criteria in untreated and treated patients. *J Hypertens* 2017; 35(12): 2388–2394.
13. Liu JE, Roman MJ, Pini R et al. Cardiac and arterial target organ damage in adults with elevated ambulatory and normal office blood pressure. *Ann Intern Med* 1999; 131(8): 564–572.
14. Trudel X, Brisson C, Larocque B, Milot A. Masked hypertension: Different blood pressure measurement methodology and risk factors in a working population. *J Hypertens* 2009; 27(8): 1560–1567.
15. Schwartz JE, Burg MM, Shimbo D et al. Clinic blood pressure underestimates ambulatory blood pressure in an untreated employer-based US population: Results from the masked hypertension study. *Circulation* 2016; 134(23): 1794–1807.
16. Wang YC, Shimbo D, Muntner P et al. Prevalence of masked hypertension among US adults with nonelevated clinic blood pressure. *Am J Epidemiol* 2017; 185(3): 194–202.
17. Myers MG. Statistical analysis as a cause of white-coat hypertension. *J Hypertens* 2017; 35(4): 707–709.
18. Cahan A, Ben-Dov IZ, Mekler J, Bursztyn M. The role of blood pressure variability in misdiagnosed clinic hypertension. *Hypertens Res* 2011; 34(2): 187–192.
19. Krause T, Lovibond K, Caulfield M, McCormack T, Williams B, Guideline Development G. Management of hypertension: Summary of NICE guidance. *BMJ* 2011; 343: d4891.
20. Kallioinen N, Hill A, Horswill MS et al. Sources of inaccuracy in the measurement of adult patients' resting blood pressure in clinical settings: A systematic review. *J Hypertens* 2017; 35(3): 421–441.
21. Rose G. Seasonal variation in blood pressure in man. *Nature* 1961; 189: 235.
22. Gavish B, Gavish L. Blood pressure variation in response to changing arm cuff height cannot be explained solely by the hydrostatic effect. *J Hypertens* 2011; 29(11): 2099–2104.
23. van Groningen LF, Adiyaman A, Elving L et al. Which physiological mechanism is responsible for the increase in blood pressure during leg crossing? *J Hypertens* 2008; 26(3): 433–437.
24. Yang L, Li L, Lewington S et al. Outdoor temperature, blood pressure, and cardiovascular disease mortality among 23,000 individuals with diagnosed cardiovascular diseases from China. *Eur Heart J* 2015; 36(19): 1178–1185.
25. Modesti PA, Morabito M, Massetti L et al. Seasonal blood pressure changes: An independent relationship with temperature and daylight hours. *Hypertension* 2013; 61(4): 908–914.
26. Weinberg I, Gona P, O'Donnell CJ et al. The systolic blood pressure difference between arms and cardiovascular disease in the Framingham Heart Study. *Am J Med* 2014; 127(3): 209–215.
27. Kollias A, Xilomenos A, Protogerou A et al. Automated determination of the ankle-brachial index using an oscillometric blood pressure monitor: Validation vs. Doppler measurement and cardiovascular risk factor profile. *Hypertens Res* 2011; 34(7): 825–830.
28. Eguchi K, Yacoub M, Jhalani J et al. Consistency of blood pressure differences between the left and right arms. *Arch Intern Med* 2007; 167(4): 388–393.
29. Ricci F, Fedorowski A, Radico F et al. Cardiovascular morbidity and mortality related to orthostatic hypotension: A meta-analysis



- of prospective observational studies. *Eur Heart J* 2015; 36(25): 1609–1617.
30. Agnoletti D, Valbusa F, Labat C et al. Evidence for a prognostic role of orthostatic hypertension on survival in a very old institutionalized population. *Hypertension* 2016; 67(1): 191–196.
  31. Bursztyjn M, Jacobs JM, Hammerman-Rozenberg A, Stessman J. Prevalence of orthostatic hypertension in the very elderly and its relationship to all-cause mortality. *J Hypertens* 2016; 34(10): 2053–2058.
  32. O'Brien E, Asmar R, Beilin L et al. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003; 21(5): 821–848.
  33. Kollias A, Stergiou GS. Automated measurement of office, home and ambulatory blood pressure in atrial fibrillation. *Clin Exp Pharmacol Physiol* 2014; 41(1): 9–15.
  34. Halfon M, Wuerzner G, Marques-Vidal P et al. Use of oscillometric devices in atrial fibrillation: A comparison of three devices and invasive blood pressure measurement. *Blood Press* 2017; 27: 1–8.
  35. Pagonas N, Schmidt S, Eysel J et al. Impact of atrial fibrillation on the accuracy of oscillometric blood pressure monitoring. *Hypertension* 2013; 62(3): 579–584.
  36. Willits I, Keltie K, Craig J, Sims A. WatchBP home A for opportunistically detecting atrial fibrillation during diagnosis and monitoring of hypertension: A NICE Medical Technology Guidance. *Appl Health Econ Health Policy* 2014; 12(3): 255–265.
  37. Chan PH, Wong CK, Pun L et al. Diagnostic performance of an automatic blood pressure measurement device, Microlife WatchBP Home A, for atrial fibrillation screening in a real-world primary care setting. *BMJ Open* 2017; 7(6): e013685.
  38. O'Brien E, Mee F, Atkins N, O'Malley K. Inaccuracy of the Hawksley random zero sphygmomanometer. *Lancet* 1990; 336(8729): 1465–1468.
  39. Mercury Sphygmomanometers in Healthcare and the Feasibility of Alternatives. 2009. [http://ec.europa.eu/health/ph\\_risk/committees/04\\_scenihr/docs/scenihr\\_o\\_025.pdf](http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_025.pdf)
  40. Consortium T. Recommended standards for assessing blood pressure in human research where blood pressure or hypertension is a major focus. *Kidney Int Rep* 2017; 2(4): 733–738.
  41. Nathan HL, Duhig K, Hezelgrave NL et al. Blood pressure measurement in pregnancy. *TOG* 2015; 17(2): 91–98.
  42. Pickering TG, Hall JE, Appel LJ et al. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: Blood pressure measurement in humans: A statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* 2005; 45(1): 142–161.
  43. Whelton PK, Carey RM, Aronow WS et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2017; 71(6): 1269–1324.
  44. Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31(7): 1281–1357.
  45. Williams JS, Brown SM, Conlin PR. Videos in clinical medicine. Blood-pressure measurement. *N Engl J Med* 2009; 360(5): e6.
  46. Sheppard JP, Stevens R, Gill P et al. Predicting Out-of-Office Blood Pressure in the Clinic (PROOF-BP): Derivation and validation of a tool to improve the accuracy of blood pressure measurement in clinical practice. *Hypertension* 2016; 67(5): 941–950.
  47. Myers MG, Valdivieso MA. Use of an automated blood pressure recording device, the BpTRU, to reduce the 'white coat effect' in routine practice. *Am J Hypertens* 2003; 16(6): 494–497.
  48. Myers MG, McInnis NH, Fodor GJ, Leenen FH. Comparison between an automated and manual sphygmomanometer in a population survey. *Am J Hypertens* 2008; 21(3): 280–283.
  49. Wohlfahrt P, Cifkova R, Movsisyan N et al. Threshold for diagnosing hypertension by automated office blood pressure using random sample population data. *J Hypertens* 2016; 34(11): 2180–2186.
  50. Godwin M, Birtwhistle R, Delva D et al. Manual and automated office measurements in relation to awake ambulatory blood pressure monitoring. *Fam Pract* 2011; 28(1): 110–117.
  51. Andreadis EA, Agaliotis GD, Angelopoulos ET et al. Automated office blood pressure and 24-h ambulatory measurements are equally associated with left ventricular mass index. *Am J Hypertens* 2011; 24(6): 661–666.
  52. Chambers LW, Kaczorowski J, O'Reilly S et al. Comparison of blood pressure measurements using an automated blood pressure device in community pharmacies and family physicians' offices: A randomized controlled trial. *CMAJ Open* 2013; 1(1): E37–E42.
  53. Myers MG, Valdivieso M, Kiss A. Use of automated office blood pressure measurement to reduce the white coat response. *J Hypertens* 2009; 27(2): 280–286.
  54. Myers MG, Godwin M, Dawes M et al. The conventional versus automated measurement of blood pressure in the office (CAMBO) trial: Masked hypertension sub-study. *J Hypertens* 2012; 30(10): 1937–1941.
  55. Group SR, Wright JT, Jr., Williamson JD et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; 373(22): 2103–2116.
  56. Cushman WC, Whelton PK, Fine LJ et al. SPRINT trial results: Latest news in hypertension management. *Hypertension* 2016; 67(2): 263–265.
  57. Kjeldsen SE, Lund-Johansen P, Nilsson PM, Mancia G. Unattended blood pressure measurements in the systolic blood pressure intervention trial: Implications for entry and achieved blood pressure values compared with other trials. *Hypertension* 2016; 67(5): 808–812.
  58. Parati G, Ochoa JE, Bilo G, Zanchetti A. SPRINT blood pressure: Sprinting back to smirk's basal blood pressure? *Hypertension* 2017; 69(1): 15–19.
  59. Myers MG, Kaczorowski J, Dolovich L et al. Cardiovascular risk in hypertension in relation to achieved blood pressure using automated office blood pressure measurement. *Hypertension* 2016; 68(4): 866–872.
  60. Andreadis EA, Papademetriou V, Geladari CV et al. Home, automated office, and conventional office blood pressure as predictors of cardiovascular risk. *J Am Soc Hypertens* 2017; 11(3): 165–70 e2.
  61. Leung AA, Daskalopoulou SS, Dasgupta K et al. Hypertension Canada's 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults. *Can J Cardiol* 2017; 33(5): 557–576.





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## INTRODUCTION

'One obvious characteristic of blood flow in arteries is that it's pulsatile'. This first sentence of the first edition of *Blood Flow in Arteries* (1) is emblematic of a current of research which has grown since the 1950s. Blood pressure (BP) is pulsatile, so two ways of expressing this phenomenon are to describe BP either through the extremes, systolic BP (SBP), the maximum of BP observed during systole, and diastolic BP (DBP), the minimum before heart contraction, or through the mean BP (MBP) and the oscillations around the mean BP (pulse pressure, PP) (2). The former view has prevailed since the invention of the cuff and mercury column by Riva-Rocci in 1896 and auscultation by Korotkoff in 1905. Since then, a wealth of evidence has been produced as to the physiology of high BP; BP being a risk factor for cardiovascular, cerebral and kidney events; and treatment of hypertension providing undisputed benefits (3). It has also obscured for half a century the latter, despite the earlier attempts at measuring pulses by Marey and Mahomet in the nineteenth century (4). Indeed, because of the increase in life expectancy, populations are ageing, and blood pressure patterns combine chronic hypertension and ageing (5). A common pattern of BP in populations is increase in SBP together with decrease in DBP, i.e. increased pulse pressure, which cannot be explained through increased peripheral resistance (6). The objective of this chapter is to describe how measurement of PP relates to the pulsatile flow in arteries, the physiology of PP, how it is measured and how it may be considered in the management of patients.

## WHAT IS PULSE PRESSURE?

PP is the difference between SBP and DBP and can be recorded at different sites along the arterial tree. PP corresponds to the pulsatile component of cardiac circulation, whereas mean BP is the theoretical pressure that would be observed if heart flow was continuous and not pulsatile (Figure 22.1). The level of mean BP is determined by cardiac output and peripheral vascular resistance.

$$\text{MBP} = \text{CO} \times \text{PVR}$$

On the other hand, PP is a complex parameter that depends on the way that left ventricular (LV) ejection volume is accommodated by large vessels in the LV outflow tract. Increased impedance to LV outflow from stiffened vessels (or reduced total arterial compliance) (7) and/or large ejection volumes, in most cases, lead to increased PP. This feature is classical, for instance, in aortic regurgitation, where ejection volume is increased because of the addition of the regurgitant volume to the normal forward-travelling volume. This leads to increased PP, which is proportional to the magnitude of regurgitation. In the absence of regurgitation, an increase in cardiac output will usually induce increased PP (e.g. in the setting of vitamin B1 deficiency, Paget's disease, anemia, hyperthyroidism, fever or arteriovenous fistula). In the absence of increased cardiac output, PP is increased during the normal (or accelerated) course of ageing, or with chronic hypertension and disease causing increased large artery stiffness, such as diabetes. In these cases, the increase in PP arises from the depleted buffering capacity of stiffened vessels, despite similar ejection volume (8).

## WHY PULSE PRESSURE NEEDS TO BE CONSIDERED

The strong tendency of PP to increase with ageing occurs predominantly after 50 years of age from the general trend towards increased SBP together with decreased DBP, and is the reason isolated systolic hypertension (ISH) is so frequent in older subjects. The demonstration that PP predicts cardiovascular events independently from SBP or DBP has been hard to achieve because of the strong collinearity between all BP components. However, this has been demonstrated by Franklin and co-workers in successive publications from the Framingham cohort (9–12) and replicated in other settings. These authors classified patients in SBP categories, and then subdivided the population according to levels of PP within each category. By doing this, they could show that irrespective of SBP, higher PP was always associated with adverse cardiovascular outcome. The association of MBP and PP in the same risk prediction model gave stronger risk estimates for predicting CVD than single

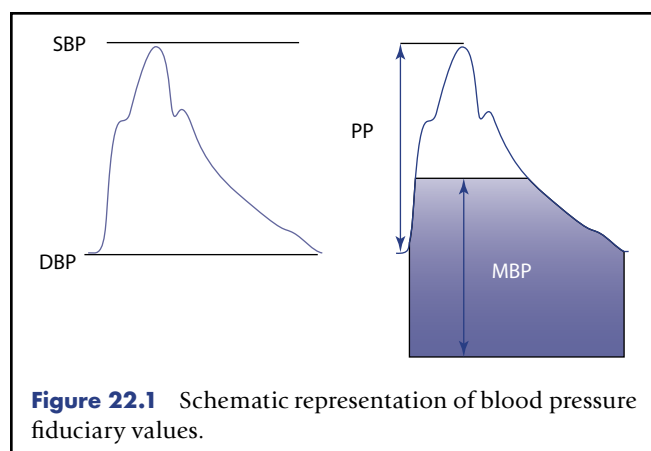


**Figure 22.1** Schematic representation of blood pressure fiducial values.

BP components (9). As with any component of BP, there is a continuum of risk, and establishing a threshold is artificial. Nonetheless, scientific societies have proposed a value of 60 mmHg as a threshold for elevated PP (13). The pertinence of this value must be modulated by the methodological issues raised later in this chapter and by the fact that PP differs according to where it is measured.

Young adults may exhibit high brachial PP in absence of concomitant elevation in central aortic PP (14). This is usually observed during so-called hyperkinetic states in early stages of essential hypertension (15). This phenomenon, later called 'spurious hypertension' (16), does not appear to be benign, as it is associated with higher rates of hypertension in the future (17), abnormally raised stroke volume and aortic stiffness (18), as well as increased risk for future cardiovascular events and mortality (19).

There are multiple links between excessive PP and CVD risk. The first and most obvious is that PP is a hallmark of ageing, and is thus associated to fatal and nonfatal CVD risk. However, even after carefully adjusting for age, PP remains significantly associated with CVD risk. This can be explained by increased impedance and LV work during ejection (20,21) ultimately leading to LV hypertrophy and LV functional decline, for which PP (especially central PP) is one of the main determinants. With advancing age, these processes are paralleled with steeper decline in DBP, potentially leading to impaired diastolic coronary perfusion (22). On the other hand, this view probably holds true only in very remodelled left ventricles (LVs) in the case of an acute drop in DBP because LV end diastolic pressure is close to DBP (23,24) and is unlikely to occur in a more general population (25).

One other aspect of PP is the effect of PP on the trophicity of arterial tissues. When compared to steady component of BP (MBP), PP exerts a powerful trophic effect of the vascular muscle cells, which increases metabolic activity and proclivity for cell hypertrophy and proliferation (26). This finding is confirmed in vivo since PP (central) is associated with carotid hypertrophy and dilatation in man (27). These phenomenon in the large arteries promote atherosclerosis. PP within the large arteries also acts on small arteries. Since the pioneering works of Baumbach and Heistad (28–30), we know that excessive pulsatility is detrimental for intracranial small arteries, leading to dilatation and hypertrophic remodelling. Similarly, the renal small arteries exhibit an extreme sensitivity to increased pulsatility (31,32). Physiologically, the stiffness of arteries increases markedly from the root of the aorta to medium-size muscular

arteries. This has consequences in terms of wave propagation and generation of proximal reflected waves, which can have detrimental effects on the LV (increased load), but at the same time may act as a filter for reducing transmission of PP to more distal small arteries (33,34). Blunting of this phenomenon is associated with increased CVD risk, at least in patients with end-stage renal disease (34).

## PERIPHERAL VERSUS CENTRAL PULSE PRESSURE

PP amplification refers to the phenomenon of a widening in PP from the central aorta to the peripheral vasculature, most commonly to the brachial artery where BP is conventionally measured. This PP widening occurs due to an increase in SBP from central to peripheral arteries, whereas DBP remains relatively similar between arterial sites. Significant within-person variability in PP amplification can occur due to individual variation in the magnitude of SBP differences between the aorta and brachial artery, which averages about 8 mmHg but can vary widely (e.g. <0 to >50 mmHg) (35) and with extreme differences of >100 mmHg observed among some patients with aortic valve regurgitation (36).

The magnitude of PP amplification can be quantified as the ratio of PP between the proximal and distal locations, and using noninvasive methods, it has been shown to decline from  $\approx 1.7$  in young adulthood to  $\approx 1.2$  in people aged over 60 years owing to a relatively greater rise in central PP with ageing compared with brachial PP (37). Ultimately, the value of central PP cannot be reliably determined from measurements of brachial PP (37,38) and this has several potential implications. Firstly, because diagnostic and hypertension management decisions may differ on the basis of central compared with brachial BP values (39,40). Secondly, central PP may respond differently to BP-lowering drugs compared with brachial PP (41), with most modern vasodilating antihypertensives having a greater central PP-lowering effect, thus risk related to BP is overestimated if only focusing on brachial BP (42). And finally, better estimates of risk may be derived from central PP compared with conventional cuff PP (43–46). This makes pathophysiological sense given the target organs are exposed to central PP rather than that in the arm (47), but nonetheless remains a controversial topic yet to be fully resolved (48,49).

## HOW TO MEASURE PULSE PRESSURE

Given that diagnostic and therapeutic decisions are made on the basis of cuff measured BP, the accuracy of BP monitors is a critical consideration. Unfortunately, most commercially available BP monitors do not provide proof of measurement accuracy according to clinical validation standards (50). In 2017, a business concerned with testing and informing consumers on the validity of medical devices, reported that from 2478 listed BP devices, only 441 (<20%) were appropriately validated (50). Even using mercury sphygmomanometry, and among validated oscillometric BP devices, there is a tendency towards systematic underestimation of (intra-arterial) brachial SBP but overestimation of DBP; altogether underappreciating the true brachial PP by an average 12 mmHg (35). The flipside of this problem is that if an individual presents

with high brachial PP (e.g.  $>60$  mmHg) we can have reasonable confidence in diagnostic sensitivity.

Growing interest towards attaining more accurate assessment of risk related to BP has led to a burgeoning of commercial devices purporting to measure central aortic BP (51). These employ a variety of methods, but with most seeking to synthesize a central aortic BP waveform using a generalized mathematical transfer function applied to a peripheral BP waveform (i.e. at the brachial or radial artery). These noninvasive devices have helped gain valuable understanding on central BP physiology, epidemiology and pharmacology, but a key problem has been reliance on the inaccurate cuff SBP and DBPs to calibrate peripheral BP waveforms. This imputes an error leading to marked underestimation of derived central PP, and also results in co-linearity between brachial SBP and central SBP such that there may be marginal advantage of central BP as a prognostic tool. However, these issues appear to be rectifiable by applying different (re)calibration approaches (52–54). Recently, an international task force made recommendations on methods for assessing and reporting the accuracy of central BP devices (55). Application of these recommendations to the measurement of central BP in a nationally representative population indicates that hypertension prevalence and control may be significantly underestimated using conventional brachial cuff BP approach (56). However, more work is needed to clarify the role of central BP devices in clinical practice.

## HOW TO USE PULSE PRESSURE AND TO 'TREAT' PULSE PRESSURE

BP monitors usually provide only the SBP and DBPs as these are the target values referred to in practice guidelines, whereas PP and MBP are seldom mentioned (13) even if they may be more meaningful from a physiological point of view. From the many epidemiological surveys which have investigated PP, a threshold of 60 mmHg has been proposed for brachial PP (Franklin); however, this value is highly dependent on the methodology used (office, 24 h ABPM, HBPM, oscillometric auscultatory, tonometry), so can only be regarded as indicative. A threshold central aortic PP of  $\geq 50$  mmHg has been proposed as a target for intervention in one study (44), but this requires confirmation.

Treatment of secondary high PP is the treatment of its cause; for example, correction of (aortic or mitral) valve regurgitation, anemia, or treatment of inflammation leads to improvement in PP. For essential high PP, then treatment is more complicated since no treatment has targeted arterial stiffness as a primary mechanism. Non-pharmacological treatment is a key factor for improving arterial stiffness and retards the increase in PP. Regular engagement in physical activity acts through multiple mechanisms, including improved metabolic balance, improved neurohormonal status (notably natriuretic peptides) and improved endothelial function (55). Pharmacological treatments should aim at controlling factors associated with arterial stiffening, such as hypertension and diabetes. Some treatments are more efficient than others (57). For instance, angiotensin-converting enzyme inhibitors and AT1R antagonists have been regularly found to be associated with reduction in PP, whereas heart-slowing molecules, such as atenolol, have a detrimental effect because of increases in the heart period and central PP. Diuretics have intermediate effect on PP

because they reduce cardiac output but increase central systolic loading. Drugs that lower PP can be difficult to identify on the basis of peripheral PP. Indeed, peripheral PP (usually brachial), incident and reflected waves coincide, and thus it is difficult to discriminate a putative beneficial effect on one component over the other. Identifying a differential effect of drugs on central versus peripheral arteries has been a real change of paradigm (58,59). The first descriptions were made by Kelly and O'Rourke when they reported that guanylate trinitrate (GTN) administered during coronary angiogram led to spectacular decrease in central SBP and virtually no change in brachial BP among some subjects (60). This concept led to the realisation of the ASCOT-CAFE trial, where 2199 hypertensives randomized either to amlodipine + perindopril or atenolol + thiazide therapy were studied for peripheral and central SBP and DBP. Despite not having baseline values, over time both groups coincided for peripheral SBP and PP, whereas a marked 4 mmHg difference was observed in favour of amlodipine + perindopril on central SBP and PP reduction. This paralleled a larger benefit, particularly for stroke in the amlodipine + perindopril arm with no direct demonstration of causality. This seminal observation was confirmed and extended by further clinical trials. The EXPLOR trial studied valsartan + amlodipine compared to atenolol + amlodipine in a forced titration scheme (59). The difference in central SBP was 4 mmHg in favour of valsartan + amlodipine, demonstrating that the adverse effect of atenolol on central BP could not be reversed by associating a vasodilator. Whether this effect on central BP translates into greater benefit is probable but remains to be proven (42,61).

## CONCLUSION

PP is an interesting parameter, directly linked to the pulsatile character of blood flow in arteries. Although the pathophysiology linked to PP elevation, i.e. increased arterial stiffness and impedance to LV outflow, shed new light on circulation, from a practical point of view, utilization of PP in clinical practice is hampered by the lack of precision of BP monitoring devices, the lack of representativity of peripheral PP for the most interesting aspects of PP physiology and the lack of precision of techniques assessing central PP. There are no trials in which treatment has been directly targeted towards PP (or arterial stiffness), thus rendering the demonstration of superiority of treating PP over the classical index of SBP difficult to achieve. One of the main limits is methodologic, since we need peripheral BP to calibrate central BP monitors, and by this we induce huge collinearities which dilute the theoretic advantages of central BP over peripheral BP. New techniques which allow direct measure of stiffness and/or central PP, without calibration, should solve this issue at short term.

## REFERENCES

1. McDonald DA. *Blood Flow in Arteries*. London: Edward Arnold; 1960; 328 p.
2. Nichols WW, McDonald DA. Wave-velocity in the proximal aorta. *Med Biol Eng* 1972; 10: 327–335.
3. Olsen MH, Angell SY, Asma S et al. A call to action and a life-course strategy to address the global burden of raised blood pressure on current and future generations: The Lancet Commission on hypertension. *Lancet* 2016; 388: 2665–2712.



4. Parati G, Mancia G. History of blood pressure measurement from the pre-Riva-Rocci era to the twenty-first century. In: Mancia G (ed.) *Handbook of Hypertension*. Elsevier, Amsterdam, The Netherlands; 2004: 2.
5. Franklin SS, Gustin Wt, Wong ND et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation* 1997; 96: 308–315.
6. Dzau VJ, Safar ME. Large conduit arteries in hypertension: Role of the vascular renin-angiotensin system. *Circulation* 1988; 77: 947–954.
7. Vennin S, Li Y, Willemet M et al. Identifying hemodynamic determinants of pulse pressure a combined numerical and physiological approach. *Hypertension* 2017; 70: 1176–1182.
8. Nichols WW, O'Rourke MF. *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*. Hodder Arnold, London; 2005.
9. Franklin SS, Lopez VA, Wong ND et al. Single versus combined blood pressure components and risk for cardiovascular disease: The Framingham Heart Study. *Circulation* 2009; 119: 243–250.
10. Franklin SS, Pio JR, Wong ND et al. Predictors of new-onset diastolic and systolic hypertension: The Framingham Heart Study. *Circulation* 2005; 111: 1121–1127.
11. Haider AW, Larson MG, Franklin SS, Levy D. Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study. *Ann Intern Med* 2003; 138: 10–16.
12. Franklin SS, Larson MG, Khan SA et al. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. *Circulation* 2001; 103: 1245–1249.
13. Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; 34: 2159–2219.
14. Herbert A, Cruickshank JK, Laurent S, Boutouyrie P. Reference values for arterial measurements C. Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk factors. *Eur Heart J* 2014; 35: 3122–3133.
15. Julius S, Nesbitt S. Sympathetic overactivity in hypertension. A moving target. *Am J Hypertens* 1996; 9: 113S–120S.
16. O'Rourke MF, Vlachopoulos C, Graham RM. Spurious systolic hypertension in youth. *Vasc Med* 2000; 5: 141–145.
17. Saladini F, Santonastaso M, Mos L et al. Isolated systolic hypertension of young- to-middle-age individuals implies a relatively low risk of developing hypertension needing treatment when central blood pressure is low. *J Hypertens* 2011; 29: 1311–1319.
18. McEniery CM, Yasmin, Wallace S et al. Increased stroke volume and aortic stiffness contribute to isolated systolic hypertension in young adults. *Hypertension* 2005; 46: 221–226.
19. Yano Y, Stamler J, Garside DB et al. Isolated systolic hypertension in young and middle-aged adults and 31-year risk for cardiovascular mortality: The Chicago Heart Association Detection Project in Industry study. *J Am Coll Cardiol* 2015; 65: 327–335.
20. Merillon JP, Fontenier GJ, Lerallut JF et al. Aortic input impedance in normal man and arterial hypertension: Its modification during changes in aortic pressure. *Cardiovasc Res* 1982; 16: 646–656.
21. Merillon JP, Motte G, Fruchaud J, Masquet C, Gourgon R. Evaluation of the elasticity and characteristic impedance of the ascending aorta in man. *Cardiovasc Res* 1978; 12: 401–406.
22. Buckberg GD, Fixler DE, Archie JP, Hoffman JJ. Experimental subendocardial ischemia in dogs with normal coronary arteries. *Circ Res* 1972; 30: 67–81.
23. Nguyen T, Do H, Pham T, Vu LT, Zuin M, Rigatelli G. Left ventricular dysfunction causing ischemia in patients with patent coronary arteries. *Perfusion* 2017; 267659117727826.
24. Elhabyan AK, Reyes BJ, Hallak O et al. Subendocardial ischemia without coronary artery disease: Is elevated left ventricular end diastolic pressure the culprit? *Curr Med Res Opin* 2004; 20: 773–777.
25. Schultz MG, Davies JE, Roberts-Thomson P, Black JA, Hughes AD, Sharman JE. Exercise central (aortic) blood pressure is predominantly driven by forward traveling waves, not wave reflection. *Hypertension* 2013; 62: 175–182.
26. Lehoux S, Castier Y, Tedgui A. Molecular mechanisms of the vascular responses to haemodynamic forces. *J Intern Med* 2006; 259: 381–392.
27. Boutouyrie P, Bussy C, Lacolley P, Girerd X, Laloux B, Laurent S. Association between local pulse pressure, mean blood pressure, and large-artery remodeling. *Circulation* 1999; 100: 1387–1393.
28. Baumbach GL. Effects of increased pulse pressure on cerebral arterioles. *Hypertension* 1996; 27: 159–167.
29. Heistad DD, Armstrong ML, Baumbach GL, Faraci FM. Sick vessel syndrome. Recovery of atherosclerotic and hypertensive vessels. *Hypertension* 1995; 26: 509–513.
30. Baumbach GL, Heistad DD. Adaptive changes in cerebral blood vessels during chronic hypertension. *J Hypertens* 1991; 9: 987–991.
31. Bidani AK, Griffin KA, Williamson G, Wang X, Loutzenhiser R. Protective importance of the myogenic response in the renal circulation. *Hypertension* 2009; 54: 393–398.
32. Briet M, Schiffrin EL. Vascular actions of aldosterone. *J Vasc Res* 2013; 50: 89–99.
33. London G, Covic A, Goldsmith D et al. Arterial aging and arterial disease: Interplay between central hemodynamics, cardiac work, and organ flow-implications for CKD and cardiovascular disease. *Kidney Int Suppl* 2011; 1: 10–12.
34. Fortier C, Mac-Way F, Desmeules S et al. Aortic-brachial stiffness mismatch and mortality in dialysis population. *Hypertension* 2015; 65: 378–384.
35. Picone DS, Schultz MG, Otahal P et al. Accuracy of cuff-measured blood pressure: Systematic reviews and meta-analyses. *J Am Coll Cardiol* 2017; 70: 572–586.
36. Kavanagh-Gray D. Comparison of central aortic and peripheral artery pressure curves. *CMAJ* 1964; 90: 1468–1471.
37. McEniery CM, Yasmin, McDonnell B et al. Central pressure: Variability and impact of cardiovascular risk factors. The Anglo-Cardiff Collaborative Trial II. *Hypertension* 2008; 6: 1476–1482.
38. Sharman JE, Stowasser M, Fassett RG, Marwick TH, Franklin SS. Central blood pressure measurement may improve risk stratification. *J Hum Hypertens* 2008; Dec 22: 838–844.
39. Borlaug BA, Olson TP, Abdelmoneim Mohamed S et al. A randomized pilot study of aortic waveform guided therapy in chronic heart failure. *J Am Heart Assoc* 2014; 3: e000745.
40. Sharman JE, Marwick TH, Gilroy D, Otahal P, Abhayaratna WP, Stowasser M. Randomized trial of guiding hypertension management using central aortic blood pressure compared with best-practice care: Principal findings of the BP GUIDE study. *Hypertension* 2013; 62: 1138–1145.
41. Kelly R, McGuire M, Healey J, Gibbs H, O'Rourke M. ECG evidence of limited myocardial infarction following coronary occlusion treated by early intravenous rt-PA infusion. *Eur Heart J* 1990; 11: 328–333.
42. Protogerou AD, Papaioannou TG, Lekakis JP, Blacher J, Safar ME. The effect of antihypertensive drugs on central blood pressure beyond peripheral blood pressure. Part I: (Patho)-physiology, rationale and perspective on pulse pressure amplification. *Curr Pharm Des* 2009; 15: 267–271.
43. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: A systematic review and meta-analysis. *Eur Heart J* 2010; 31: 1865–1871.
44. Roman MJ, Devereux RB, Kizer JR et al. High central pulse pressure is independently associated with adverse cardiovascular outcome the strong heart study. *J Am Coll Cardiol* 2009; 54: 1730–1734.
45. Cheng H-M, Chuang S-Y, Sung S-H et al. Derivation and validation of diagnostic thresholds for central blood pressure measurements based on long-term cardiovascular risks. *J Am Coll Cardiol* 2013; 62: 1780–1787.
46. Kollias A, Lagou S, Zeniodi ME, Boubouchairopoulou N, Stergiou GS. Association of central versus brachial blood pressure with target-organ damage: Systematic review and meta-analysis. *Hypertension* 2015; 67: 183–190.
47. Subherwal S, de las Fuentes L, Waggoner AD, Heuerman S, Spence KE, Davila-Roman VG. Central aortic pressure is independently associated with diastolic function. *Am Heart J* 2010; 159: 1081–1088.
48. Sharman JE. Central pressure should be used in clinical practice. *Artery Research* 2015; 9: 1–7.
49. Mitchell GF. Central pressure should not be used in clinical practice. *Artery Research* 2015; 9: 8–13.
50. Stergiou GS, Alpert B, Mieke S et al. A Universal Standard for the Validation of Blood Pressure Measuring Devices. Association for the Advancement of Medical Instrumentation/European Society of Hypertension/International Organization for Standardization (AAMI/ESH/ISO) Collaboration Statement 2018.
51. Millasseau S, Agnoletti D. Non-invasive estimation of aortic blood pressures: A close look at current devices and methods. *Curr Pharm Des* 2015; 21: 709–718.



52. Cheng HM, Sung SH, Chuang SY et al. Diagnostic performance of a stand-alone central blood pressure monitor: Application of central blood pressure in the diagnosis of high blood pressure. *Am J Hypertens* 2014; 27: 382–391.
53. Papaioannou TG, Karageorgopoulou TD, Sergeantanis TN et al. Accuracy of commercial devices and methods for noninvasive estimation of aortic systolic blood pressure a systematic review and meta-analysis of invasive validation studies. *J Hypertens* 2016; 34: 1237–1248.
54. Wassertheurer S, Baulmann J. Assessment of systolic aortic pressure and its association to all cause mortality critically depends on waveform calibration. *J Hypertens* 2015; 33: 1884–1888.
55. Sharman JE, Avolio AP, Baulmann J et al. Validation of non-invasive central blood pressure devices: ARTERY Society Task Force Consensus Statement on Protocol Standardization. *Eur Heart J* 2017; 38: 2805–2812.
56. Chuang SY, Chang HY, Cheng HM, Pan WH, Chen CH. Prevalence of hypertension defined by central blood pressure measured using a type II device in a nationally representative cohort. *Am J Hypertens* 2018; 31(3): 346–354.
57. Boutouyrie P, Lacolley P, Briet M et al. Pharmacological modulation of arterial stiffness. *Drugs* 2011; 71: 1689–1701.
58. Williams B, Lacy PS, Thom SM et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: Principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006; 113: 1213–1225.
59. Boutouyrie P, Achouba A, Trunet P, Laurent S, Group ET. Amlodipine-valsartan combination decreases central systolic blood pressure more effectively than the amlodipine-atenolol combination: The EXPLOR study. *Hypertension* 2010; 55: 1314–1322.
60. Kelly RP, Gibbs HH, O'Rourke MF et al. Nitroglycerin has more favourable effects on left ventricular afterload than apparent from measurement of pressure in a peripheral artery. *Eur Heart J* 1990; 11: 138–144.
61. Manisty CH, Hughes AD. Meta-analysis of the comparative effects of different classes of antihypertensive agents on brachial and central systolic blood pressure, and augmentation index. *Br J Clin Pharmacol* 2013; 75: 79–92.



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## INTRODUCTION

The gold standard for measuring blood pressure (BP) and diagnosing hypertension is the brachial cuff, thus favouring a distal site accessible to noninvasive measurement. However, two concepts have gained an important audience recently: pressure amplification between central and peripheral arteries, and higher damaging effect of local BP than brachial BP on target organs in hypertensive patients. An increasing number of physiological studies, as well as pathophysiological, epidemiological and pharmacological studies, have underlined the importance of measuring not only brachial systolic and pulse pressures, but also central systolic and pulse pressures. The aims of this chapter are (a) to detail the hemodynamic characteristics of the arterial circulation in order to explain why it is important to measure central BP, (b) to describe the various noninvasive methods currently available to measure central BP, (c) to discuss the concepts of intermediate and surrogate endpoints in order to determine if they are applicable to central BP, and (d) to describe how drugs can reduce abnormally high central BP.

## PATHOPHYSIOLOGY OF CENTRAL BLOOD PRESSURE AND WAVE REFLECTION IN HYPERTENSION

### HEMODYNAMIC AND REFLECTION OF PRESSURE WAVES

During ventricular contraction, part of the stroke volume is forwarded directly to the peripheral tissues, and part of it is momentarily stored in the aorta and central arteries, stretching the arterial walls and elevating local blood pressure (Figure 23.1). Part of the energy produced by the heart is diverted for the distension of arteries and is 'stored' in the vessel walls. During diastole, the 'stored' energy recoils the aorta, squeezing the accumulated blood forward into the peripheral tissues, ensuring a continuous flow (Figure 23.1). To decrease the cardiac work during ventricular ejection, the energy necessary for

arterial distension and recoil should be low, that is, for a given stroke volume, the pressure rise should be as low as possible (17). The efficiency of this function depends on the stiffness and geometry of the arteries (11,17). When the stiffness is low, the arterial wall opposes low resistance to distension and the pressure effect is minimized. When the arterial system is rigid and cannot be stretched, the entire stroke volume will flow through the arterial system and peripheral tissues only during systole with two consequences: intermittent flow and short capillary transit time with reduced metabolic exchanges.

The ejection of blood into the aorta generates a wave that propagates along the aorta towards the peripheral arterial tree. The velocity of wave propagation along the aorta, that is, pulse wave velocity (PWV), is dependent on factors determining (a) the displacement of blood along the axis of the vessel, with inertia being the most important effect in large arteries; and (b) the transverse displacement of the vessel wall, i.e. the stiffness of the vessel (the stiffer the arterial wall the higher the PWV) (17). The arterial pressure waveform which is measured centrally is a composite of the forward pressure wave created by ventricular contraction and a reflected wave (11,17) (Figure 23.2). Indeed, the arterial tree is not a simple tube but a complex structure with a reflection site at its distal end. From the heart towards the periphery, arteries continuously decrease in diameter (i.e. geometric taper) and increase in stiffness (i.e. elastic taper, also named 'arterial stiffness gradient') while also continuously branching (11).

The stiffness gradient, together with the geometric taper, local arterial branching and lumen narrowing, creates an impedance mismatch causing partial reflections of forward pressure waves travelling back to the central aorta (reflected wave) (11,17) (Figure 23.3). The wave reflections will considerably change the pressure wave amplitude and shape along the arterial tree. Forward and reflected pressure waves overlap, and the final amplitude and shape of the pulse pressure wave are determined by the phase relationship (the timing) between these component waves. The overlap between the two waves depends on the site of pressure recording along the arterial tree. Peripheral arteries are close to reflection sites and the reflected wave occurs at the impact of forward wave; that is, the waves are in phase, producing an additive effect.

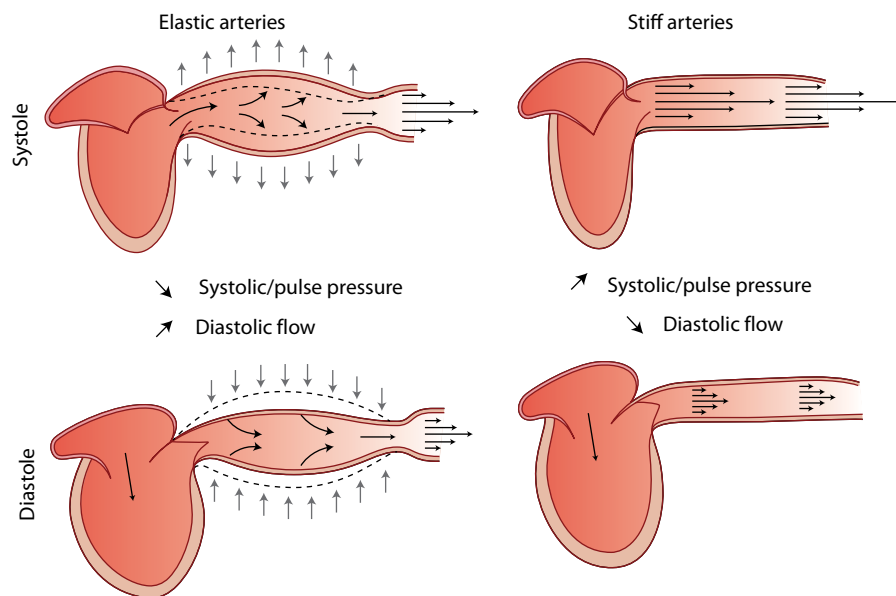


**Figure 23.1** Schematic representation of the role of arterial stiffness on assuring continuous blood flow through the peripheral circulation, and how the aortic stiffening leads to increased SBP and PP. (Adapted from Briet M et al. *Kidney Int* 2012; 82: 388–400 (6). With permission.)

The ascending aorta and central arteries are distant from reflecting sites, and the return of the reflected wave is variably delayed depending on PWV and travelling distances (Figures 23.2 and 23.3) (17). In the aorta or central arteries, the forward and reflected waves are not in phase. In subjects with low PWV, reflected waves impact on central arteries during end-diastole, increasing the aortic pressure in early diastole and not during systole. This is physiologically advantageous, since the increased diastolic pressure boosts the coronary perfusion without increasing the LV pressure load.

Pressure waves are reflected from the periphery, mainly at branch points or sites of impedance mismatch. The

reflection pattern is thus complex but may be seen as a 'net' or 'effective' reflection pattern, where all the forward and backward running waves seem to add up to one single forward and backward wave, representing the global effect of all reflections present (17). The phenomenon of wave reflection can be quantified through the augmentation index (AIx) – defined as the difference between the second (P2) and first (P1) systolic peaks ( $P2 - P1 = AP$ , i.e. augmentation pressure) expressed as a percentage of pulse pressure (PP) (Figure 23.4).

Thus, apart from a high PWV, changes in reflection sites can also influence central systolic blood pressure (SBP), PP and AIx. The major determinant of central SBP and PP is, by definition, the forward pressure wave, since the reflected wave can never be higher than the forward wave (17). In clinical investigation, not only DBP and height, which are related to total peripheral resistance and reflection sites, but also age and aortic PWV are the main determinants of AIx.

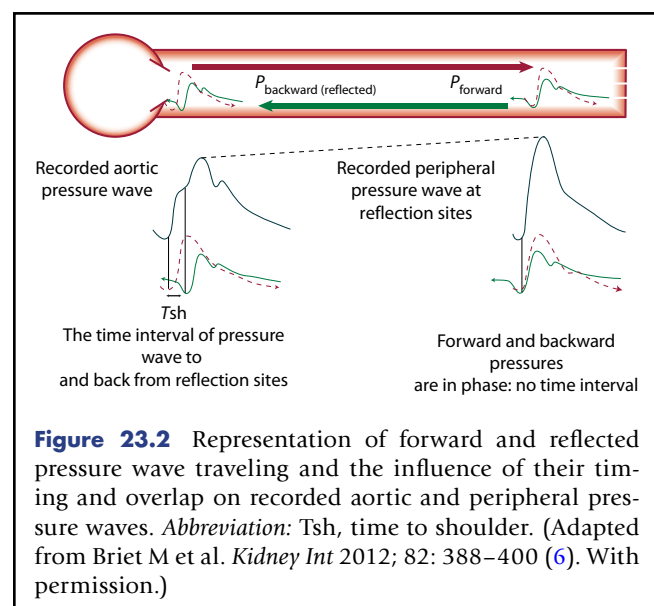


**Figure 23.2** Representation of forward and reflected pressure wave traveling and the influence of their timing and overlap on recorded aortic and peripheral pressure waves. Abbreviation: Tsh, time to shoulder. (Adapted from Briet M et al. *Kidney Int* 2012; 82: 388–400 (6). With permission.)

## AMPLIFICATION PHENOMENON

When SBP is recorded invasively and simultaneously in the aortic arch and at multiple peripheral sites, it is possible to detect an 'amplification phenomenon', i.e. under resting conditions in healthy men, brachial SBP is about 10% higher than aortic SBP (Figure 23.3). Indeed, in the presence of arterial stiffness gradient (aortic PWV < peripheral PWV) partial pressure wave reflection occurs distant from microcirculation and returns at low PWV to the aorta in diastole, thus the reflected wave arrives back at the aortic root during late systole, whereas at the site of the peripheral artery (i.e. brachial artery), the pressure wave travels rapidly and the reflected wave (from peripheral branching sites and small arteries) arrives at the recording site

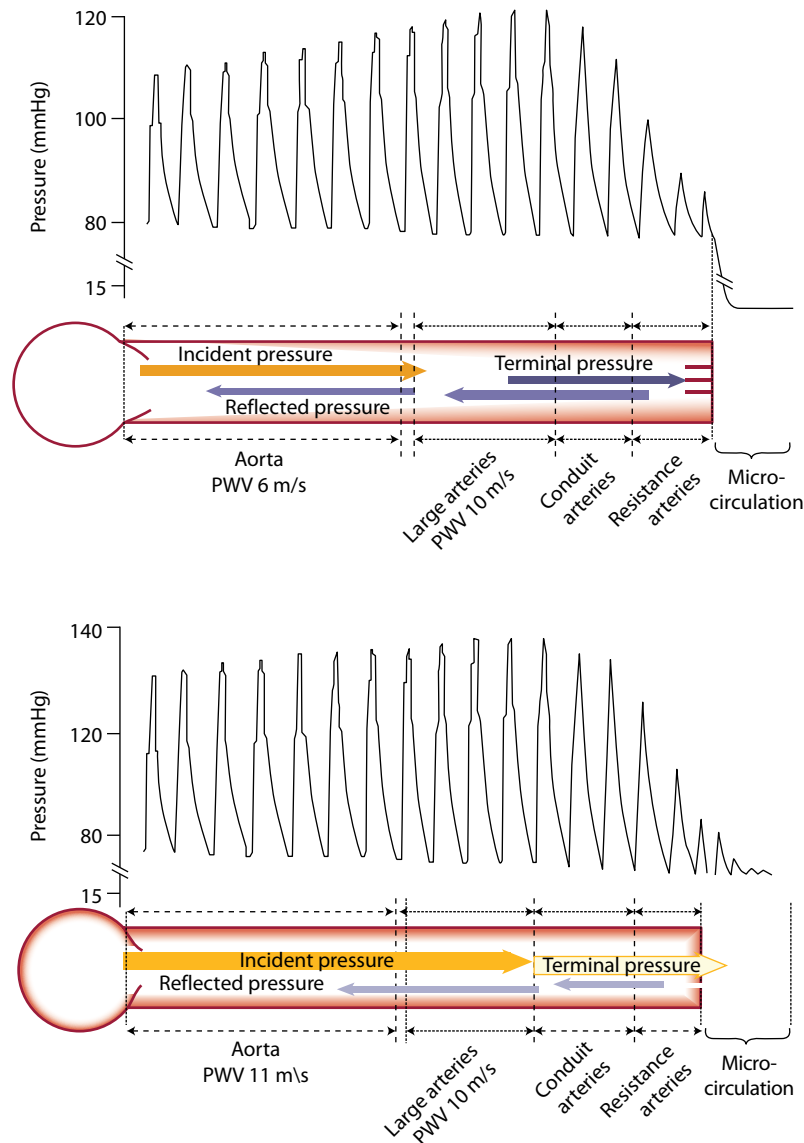


**Figure 23.3** Upper panel: In the presence of arterial stiffness gradient (aortic PWV < peripheral PWV) partial pressure wave reflection occurs distant from microcirculation and returns at low PWV to the aorta in diastole maintaining central-to-peripheral amplification. Partial pressure wave reflections limit the transmission of pulsatile pressure energy to the periphery and protect the microcirculation. Lower panel: When the stiffness gradient disappears or is inverted (aortic PWV > peripheral PWV), pulsatile pressure is not sufficiently dampened and is transmitted, thus damages the microcirculation. In parallel, the central-to-peripheral pressure amplification is attenuated. (Adapted from Briet M et al. *Kidney Int* 2012; 82: 388–400 (6). With permission.)

in early systole, raising brachial SBP; thus, central SBP is lower than distal SBP, leading to the so-called 'central-to-peripheral amplification'. By contrast, when the stiffness gradient disappears or is inverted (aortic PWV > peripheral PWV), pulsatile pressure is not sufficiently dampened at the central level, and the central-to-peripheral pressure amplification is attenuated (9) (Figure 23.3).

The amplification phenomenon is attenuated by ageing (9) because of arterial stiffening. Indeed, by favouring early wave reflections, arterial stiffening increases peak- and end-systolic pressures in the ascending aorta,

increasing myocardial pressure load (left ventricular hypertrophy) and oxygen consumption, decreasing the diastolic blood pressure and subendocardial blood-flow. Thus central SBP is higher in elderly subjects than in young subjects and closer to the brachial SBP value, reducing the difference (9). Indeed, at the site of the brachial artery, arterial stiffness is not influenced by age (9), and the timing of forward and reflected waves is similar to those in younger subjects. In conclusion, the true value of central BP cannot be reliably estimated using standard brachial cuff BP (14,17,19).



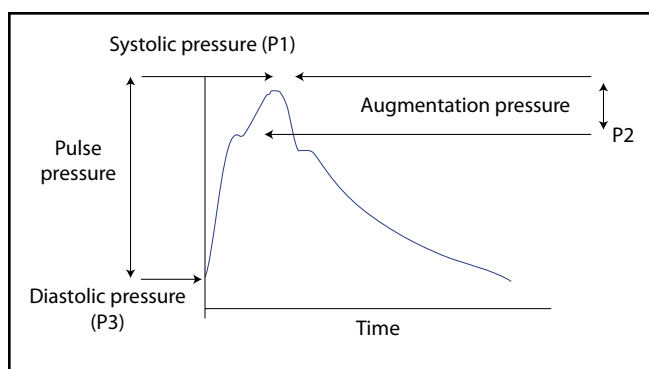


**Figure 23.4** The phenomenon of wave reflection can be quantified through the augmentation index (AIx) – defined as the difference between the second (P2) and first (P1) systolic peaks ( $P2 - P1 = AP$ , i.e. augmentation pressure) expressed as a percentage of PP:  $AIx = AP/PP$ . (Adapted from Laurent S et al. *Eur Heart J* 2006; 27: 2588–2605 (10). With permission.)

### CENTRAL BLOOD PRESSURE IS INDEPENDENTLY RELATED TO TARGET-ORGAN DAMAGE

The hemodynamic mechanisms leading to end-organ damage are complex, probably organ-specific and not fully understood (18,24). They likely include not only a direct effect of pressure pulsatility on conduit artery but also an effect on smaller resistive arteries. Indeed, pressure pulsatility can stimulate hypertrophy, remodelling (increased media-to-lumen ratio) or rarefaction in the microcirculation, leading to increased resistance to mean flow. Significant relationships have been demonstrated between brachial PP and either glomerular filtration rate (GFR), microalbuminuria, or white matter lesions (6,18); between arterial stiffness and either GFR (6), urinary albumin, retinal arteriolar narrowing, white matter lesions or cognitive function (16,18); and between carotid stiffness and GFR. Although not all these relationships are independent of confounding factors, there is a large amount of evidence for linking the pulsatility of BP to target-organ damage (18,24).

The damaging effect of central BP on target organs should theoretically be more important than that of brachial BP, because the blood pressure regimen, to which arteries and organs are chronically exposed, is central BP and not peripheral BP. Cardiac hypertrophy as well as left ventricular systolic and diastolic dysfunction, is related to elevated central augmentation index, systolic BP and PP independent of standard cuff BP (22). In the same way, adverse effects on the structure (e.g. carotid wall hypertrophy, intima media thickness and plaque score) and function (e.g. compliance) of large central arteries is more contingent on central arterial pressure than on conventional brachial BP (3). There is also very good evidence that central (carotid) artery lumen size, function and PP separately relate to kidney function in terms of glomerular filtration rate, albuminuria and progression of chronic kidney disease (6). Brain atrophy, silent subcortical infarcts and cognitive impairment all independently correlate with central hemodynamic factors (16,18). The transmission of excessive pressure or flow pulsatility into the carotid

circulation could trigger brain microvascular damage and remodelling (16). Whether central hemodynamics could provide more accurate prognostic information on the progression of target-organ damage beyond cuff BP remains to be determined in longitudinal studies (25).

### METHODS FOR DETERMINING CENTRAL BLOOD PRESSURE AND WAVE REFLECTION

A large number of reviews have made recommendations for adequate measurements of central BP (8,10,15,19,26,27,29). Arterial pressure waveform should be analysed at the central level, that is, the ascending aorta, since it represents the true load imposed on the heart, the brain and the kidney, and more generally to central large artery walls. Table 23.1 details the various methods currently used for determining central BP. The pressure waveform can be recorded noninvasively with a pencil-type probe incorporating a high-fidelity Millar strain gauge transducer (SPT-301, Millar Instruments). The most widely used approach is to perform radial artery tonometry and then apply a transfer function (Sphygmocor, AtCor, Sydney Australia) to calculate the aortic pressure waveform from the radial waveform (10). Indeed, the radial artery is well supported by bony tissue, making optimal applanation easier to achieve.

Aortic pressure waveform can also be estimated from the common carotid waveform (Table 23.1). Carotid tonometry requires a higher degree of technical expertise (3,4,10), but a transfer function is not necessary since the arterial sites are very close and waveforms are similar (17). A large number of pathophysiological and pharmacological studies have been published using these methods (3–5,13,20,31).

In addition to methods determining the pressure waveform at the central site, novel methods have been developed which aim at determining the discrete value of central SBP using the second systolic peak (SBP2) on the radial or brachial pressure waveforms (2,21,30) (Table 23.1).

### AMBULATORY CENTRAL BP MONITORING

Several apparatus using brachial cuff methodology claimed a reliable measurement of central BP along the 24 h (21,30). However, none convincingly demonstrated that the BP values which were recorded under ambulatory conditions truly reflect central BP. Variable results have been obtained, as far as target-organ damage is concerned. For instance, although Protogerou et al. (21) observed that 24-h average aortic SBP had higher discriminatory ability of to detect the presence of LVH than 24-h average brachial SBP, other studies did not confirm this observation (30).

### CENTRAL BLOOD PRESSURE AND WAVE REFLECTION AS INTERMEDIATE OR SURROGATE ENDPOINT

Several longitudinal epidemiological studies have demonstrated the predictive value of central pulse pressure and

**Table 23.1** Device and methods used for estimating central blood pressure, classified through the arterial segment used for pressure wave recording

| Year of first publication                | Device                 | Method                                 | Company          | Parameters                     |
|------------------------------------------|------------------------|----------------------------------------|------------------|--------------------------------|
| <i>Radial artery pressure waveform</i>   |                        |                                        |                  |                                |
| 1990                                     | Sphygmocor®*           | Tonometer, GTF                         | Atcor Medical    | cSBP, cPP, cAlx                |
| 1997                                     | Cardiovasc. Eng. Inc®* | Tonometer, cardiac echo, impedance     | Cardiovasc. Eng. | cSBP, cPP, cAlx<br>Zc, fP, bP  |
| 2004                                     | PulsePen               | Tonometer, direct                      | DiaTecne srl     | cSBP, cPP, cAlx                |
| 2009                                     | Omron HEM-9001A I®     | Tonometer                              | Omron            | cSBP, rAlx                     |
| 2012                                     | BPro®                  | Tonometer                              | HealthSTATS      | rAlx                           |
| <i>Brachial artery pressure waveform</i> |                        |                                        |                  |                                |
| 2010                                     | Arteriograph®          | Oscillometric, Add. Infl.              | TensioMed        | cSBP, cPP, cAlx,               |
| 2010                                     | Mobil-O-Graph®         | Oscillometric, ARC Solver-PVP software | IEM              | cSBP, cPP, cAlx,<br>Zc, fP, bP |
| 2010                                     | BPLab®                 | Oscillometric                          | BP Lab           | cSBP, cPP, cAlx                |
| 2012                                     | Centron cBP301         | Oscillometric                          | Centron          | cSBP, cPP, cAlx                |
| 2012                                     | Cardioscope II         | Oscillometric, Add. Infl.              | Pulsecor         | cSBP, cPP, cAlx                |
| 2013                                     | Vicorder®              | Oscillometric                          | Skidmore         | cSBP, cPP, cAlx                |
| <i>Carotid artery pressure waveform</i>  |                        |                                        |                  |                                |
| 1984                                     | Millar® strain gauge*  | Tonometer, direct                      | Millar           | cSBP, cPP, cAlx                |
| 2004                                     | PulsePen               | Tonometer, direct                      | DiaTecne srl     | cSBP, cPP, cAlx                |

Source: Adapted from Laurent S, Boutouyrie P. How to estimate central blood pressure? In *Dialogues in Cardiovascular Medicine*, 2015.

\*Apparatus used in pioneering epidemiological studies showing the predictive value of central BP for CV events.

Abbreviations: cSBP, central systolic blood pressure; cPP, central pulse pressure; cAlx, central augmentation index; rAlx, radial artery augmentation index; Zc, characteristic impedance; fP, forward pressure wave; bP, backward pressure wave; Add. Infl., additional inflation; PVP, pulse volume plethysmography; N.A., not available.

augmentation index as intermediate endpoints, that is, the higher the central pulse pressure and augmentation index, the higher the number of CV events.

## CENTRAL BLOOD PRESSURE HAS AN INDEPENDENT PREDICTIVE VALUE OF CV EVENTS

Since the early 2000s, several longitudinal studies have shown that central PP had independent predictive value for all-cause and CV mortality. Central augmentation index and pulse pressure, either directly measured by carotid tonometry (23) or estimated using a transfer function from radial artery tonometry (31), were both independent predictors of all-cause mortality in end-stage renal disease patients (23), in patients undergoing percutaneous coronary intervention and in the hypertensive patients of the CAFE study (31).

Eleven studies performed in populations at various CV risk, totaling 5648 subjects with a mean follow-up of 3.8 y, were included in a meta-analysis (28). In six of them,

the RR of total CV events for an increase of central PP by 10 mmHg was 1.14 (1.06–1.21). It was 1.09 (1.04–1.14) for central SBP. The various mechanisms by which an increase in central pulse pressure generates higher risk of cardiac and cerebrovascular events have been described above. Central BP can thus be considered as an intermediate endpoint for CV events.

## CENTRAL PULSE PRESSURE AS A SURROGATE ENDPOINT

A surrogate endpoint is a biomarker that is intended as a substitute for a clinical endpoint. In order to be considered as a surrogate endpoint of cardiovascular events, a biomarker should satisfy several criteria, such as proof of concept, prospective validation, incremental value, clinical utility, clinical outcomes, cost-effectiveness, ease of use, methodological consensus and reference values.

Although a large number of studies and several reviews (14,16,23,31) demonstrated that central PP was increased in various pathophysiological conditions, and

had predictive value for all-cause and CV mortality, only a marginal superiority of central PP over brachial PP for predicting CV events was observed in a meta-analysis (28), and there was no superiority of central SBP over brachial SBP. Additional studies, not included in the meta-analysis, also failed to show higher predictive values of central PP compared to brachial PP (10). To our knowledge, no study has demonstrated that patients at intermediate risk could be reclassified into a higher or a lower CV risk, when central BP (either PP or SBP) was measured (29).

Large randomized clinical trials, aiming at reducing both central BP and CV events, are needed in order to infer causality between central BP reduction and CV risk reduction. The only randomized intervention trial with recording of central BP and CV events was the Conduit Artery Function Evaluation (CAFE) study, an ancillary study of the ASCOT study (7) in 2199 patients with hypertension and multiple CV risk factors (31). The CAFE study showed that a therapeutic regimen based on amlodipine was more effective than an atenolol-based regimen to lower central BP, despite similar brachial SBP between treatment groups. Because the ASCOT study (7) showed that the amlodipine-based regimen prevented more major CV events than the atenolol-based regimen, it was tempting to attribute this superiority, at least in part, to a higher efficacy on the reduction in central BP. However, such a conclusion cannot be drawn since central BP was not measured at baseline in the CAFE study (31), and thus no change in central BP could be calculated.

There is an ongoing controversy on whether the lack of higher predictive value of central BP compared to brachial BP reflects a true pathophysiological issue or is related to the method used for central BP measurement, including calibration (19,26,27). To address the latter issue, an international task force was convened (26) testing new and preceding devices in a uniform fashion with comparable protocols.

## REFERENCE VALUES AND GUIDELINES

Reference values for central BP (9) have been established in 18,183 healthy subjects and a larger population of 27,253 subjects with CV risk factors.

The 2013 ESH-ESC Guidelines for the Management of Hypertension (12) and a position paper from the European Society of Cardiology (ESC) Working Group on Peripheral Circulation (29) considered that although the measurement of central BP and augmentation index is of great interest for mechanistic analyses in pathophysiology, pharmacology and therapeutics, more investigation is necessary before recommending their routine clinical use.

## ISOLATED HYPERTENSION IN THE YOUNG

A number of young, healthy males have elevated values of brachial SBP (above or equal to 140 mmHg) and normal values of brachial DBP (below 90 mmHg). Measurement of central BP may help diagnosing spurious hypertension if central SBP is normal, according to the reference values data (10). If there is no target-organ damage, then a simple follow-up is necessary (12). Since the reference values data (10) give for each decade of age and category of BP the

10th, 25th, 75th and 90th percentiles for normal values, it is possible to diagnose high-normal central BP, which is an indication for a closer follow-up.

According to the 2013 ESH-ESC Guidelines (12), 'no evidence is available that young patients with ISH benefit from antihypertensive treatment; on the contrary there are prospective data that the condition does not necessarily proceed to systolic/diastolic hypertension. On the basis of current evidence, these young individuals can only receive recommendations on lifestyle, but because available evidence is scanty and controversial they should be followed closely'.

## PHARMACOLOGY OF CENTRAL BLOOD PRESSURE AND WAVE REFLECTION IN HYPERTENSION

A large number of publications and several reviews (4,5,10,13,20) reported the changes in central BP and wave reflections after various pharmacological treatments. Pharmacological treatments which are able to reduce central BP and wave reflections include (a) all antihypertensive treatments, such as diuretics, beta-blockers, ACE inhibitors, angiotensin II receptor blockers (ARBs) and calcium channel blockers (CCBs); (b) treatments of congestive heart failure, such as ACE inhibitors, nitrates and aldosterone antagonists; and (c) advanced glycation end-product (AGE)-breakers, such as alagebrium (ALT-711).

## DIFFERENTIAL CENTRAL AND BRACHIAL BP RESPONSES TO ANTIHYPERTENSIVE MEDICATIONS

Whether pharmacological classes, and specific molecules within a given pharmacological class, differ in their ability to lower central BP, has been addressed in several studies (4,5,10,13,20). Protogerou et al. (20) analysed the ability of drug treatment to lower central BP beyond the reduction in peripheral (brachial) BP by computing the effects of drugs on BP amplification, according to either its absolute (peripheral PP *minus* central PP, in mmHg) or relative (peripheral PP/central PP) expression. There are several mechanisms by which drugs may differently alter central and peripheral BP, thus BP amplification. They include large artery stiffness, vascular resistance, stroke volume and heart rate.

The pharmacological classes which induce a greater decrease in central SBP relative to brachial SBP, in other words which increase SBP amplification are mainly angiotensin-converting enzyme inhibitors (ACEIs), ARBs and CCBs, whereas diuretics are less efficacious (5,10). Non-vasodilating beta-blockers (such as propranolol and atenolol) are the least effective agents for reducing central SBP/PP. Instead of increasing SBP amplification, they reduce it by inducing a lower decrease in central SBP relative to brachial SBP (4,31). Mechanisms explaining the possible deleterious effects of beta-blockers in general, and atenolol in particular, include the reduction in heart rate, the lack of reduction of total peripheral resistance and sympathetic drive, and a possible 'pro-fibrotic effects' on large

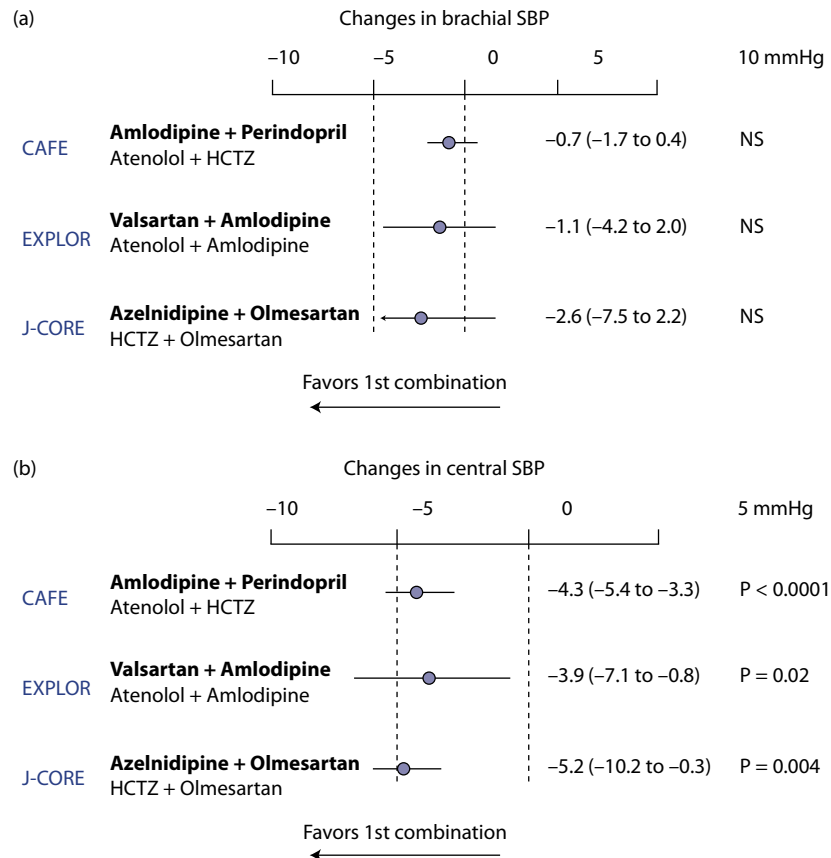


**Figure 23.5** Differential effects of antihypertensive combination therapies on brachial SBP (a) and central SBP (b), determined during the CAFE (31), EXPLOR (4) and J-CORE (13) studies.

arteries. Nitrates, which are not indicated for hypertension, increase SBP amplification (5,10).

Combination therapies exert also differential effects on brachial and central BP (Figure 23.5). The available evidence, originating from the CAFE (31), EXPLOR (4) and J-CORE (13) studies, indicates that this is a combination of CCB and either ACEI or ARB, which is the most effective for reducing central SBP, for a given reduction in brachial SBP.

### IMPROVEMENT IN TARGET-ORGAN DAMAGE IN RELATION TO CHANGES IN CENTRAL BP

If central BP is to be considered appropriate for hypertension management, it is necessary for improvement in end-organ characteristics, with therapy to be more strongly influenced by the changes in central BP (e.g. relief of 'central hypertension') rather than the changes in brachial BP (24,25). Several studies have reported such findings, including the randomised double-blind REASON study (1), in which the low-dose combination perindopril/indapamide was more effective than atenolol in reducing left ventricular mass through a higher reduction in central PP.

Two studies investigated the associated changes in large arteries. In a randomized study comparing celiprolol and enalapril over 9 months, the reduction in carotid

intima media thickness was principally determined by the reduction in carotid PP after adjustment on brachial PP, although no significant difference was observed between drugs (5). In a randomized study comparing the effect of amlodipine/valsartan combination to amlodipine/atenolol combination on central and peripheral BP and aortic stiffness over 6 months, the reduction in carotid-femoral PWV was positively associated with the reduction in aortic SBP but not with the reduction in brachial BP (4).

### CONCLUSION

This chapter highlights the importance of central BP and wave reflection, not only for assessing CV risk, but also for predicting CV outcomes. The concepts of (a) pressure amplification between central and peripheral arteries, and (b) higher damaging effect of local BP than brachial BP on target organs in hypertensive patients, are well supported by the findings of pathophysiological and pharmacological studies. Although the noninvasive measurement of central BP appears now as a major tool for clinical research, more pharmacological and outcome studies are needed in order to establish central BP as a true surrogate endpoint deserving to be listed among the various parameters of the routine workup in hypertensive patients.



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## REFERENCES

1. Asmar RG, London GM, O'Rourke ME et al. Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patient: A comparison with atenolol. *Hypertension* 2001; 38: 922–926.
2. Baulmann J, Schillings U, Rickert S et al. A new oscillometric method for assessment of arterial stiffness: Comparison with tonometric and piezo-electronic methods. *J Hypertens* 2008; 26: 523–528.
3. Boutouyrie P, Bussy C, Lacolley P et al. Association between local pulse pressure, mean blood pressure, and large-artery remodeling. *Circulation* 1999; 100: 1387–1393.
4. Boutouyrie P, Achouba A, Trunet P et al. The amlodipine-valsartan combination decreases central systolic blood pressure more effectively than atenolol-amlodipine: The EXPLOR study. *Hypertension* 2010; 55: 1314–1322.
5. Boutouyrie P, Lacolley P, Briet M et al. Pharmacological modulation of arterial stiffness. *Drugs* 2011; 71: 1689–1701.
6. Briet M, Boutouyrie P, Laurent S, London G. Arterial stiffness and pulse pressure in CKD and ESRD. *Kidney Int* 2012; 82: 388–400.
7. Dahlöf B, Sever PS, Poulter NR et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding Bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): A multicentre randomised controlled trial. *Lancet* 2005; 366: 895–906.
8. Giannattasio C. How to assess central arterial blood pressure? *J Hypertens* 2003; 21: 495–496.
9. Herbert A, Cruickshank K, Laurent S et al. Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk-factors. *Eur Heart J* 2014; 35: 3122–3133.
10. Laurent S, Cockcroft J, Van Bortel L et al. Expert consensus document on arterial stiffness: Methodological aspects and clinical applications. *Eur Heart J* 2006; 27: 2588–2605.
11. Laurent S, Boutouyrie P. The structural factor in hypertension: Large and small artery alterations. *Circ Res* 2015; 116: 1007–1021.
12. Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; 34: 2159–2219.
13. Matsui Y, O'Rourke MF, Ishikawa J et al. Association of changes in ambulatory arterial stiffness index and pulse wave velocity during antihypertensive treatment: The J-CORE study. *Am J Hypertens* 2012; 25: 862–868.
14. McEniery CM, Yasmin, McDonnell B et al. Central pressure: Variability and impact of cardiovascular risk factors. The Anglo-Cardiff Collaborative Trial II. *Hypertension* 2008; 6: 1476–1482.
15. McEniery CM, Cockcroft JR, Roman MJ et al. Central blood pressure: Current evidence and clinical importance. *Eur Heart J* 2014; 35: 1719–1725.
16. Mitchell GF, van Buchem MA, Sigurdsson S et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: The Age, Gene/Environment Susceptibility-Reykjavik Study. *Brain* 2011; 134: 3398–3407.
17. Nichols WW, O'Rourke MF. *McDonald's Blood Flow in Arteries; Theoretical, Experimental and Clinical Principles*. 6th ed. Hodder Arnold; 2011: 755 pages.
18. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney. Cause and logic of therapy. *Hypertension* 2005; 46: 200–204.
19. Picone DS, Schultz MG, Otahal P et al. Accuracy of cuff-measured blood pressure: Systematic reviews and meta-analyses. *J Am Coll Cardiol* 2017; 70: 572–586.
20. Protogerou AD, Stergiou GS, Vlachopoulos C et al. The effect of antihypertensive drugs on central blood pressure beyond peripheral blood pressure. Part II: Evidence for specific class-effects of antihypertensive drugs on pressure amplification. *Curr Pharm Des* 2009; 15: 272–289.
21. Protogerou AD, Argyris AA, Papaioannou TG et al. Left-ventricular hypertrophy is associated better with 24-h aortic pressure than 24-h brachial pressure in hypertensive patients: The SAFAR study. *J Hypertens* 2014; 32: 1805–1814.
22. Roman MJ, Devereux RB, Kizer JR et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: The Strong Heart Study. *Hypertension* 2007; 50: 197–203.
23. Safar ME, Blacher J, Pannier B et al. Central pulse pressure and mortality in end-stage renal disease. *Hypertension* 2002; 39: 735–738.
24. Safar ME, Nilsson PM, Blacher J, Mimran A. Pulse pressure, arterial stiffness, and end-organ damage. *Curr Hypertens Rep* 2012; 14: 339–344.
25. Sharman JE, Marwick TH, Abhayaratna WP, Stowasser M. Rationale and design of a randomized study to determine the value of central Blood Pressure for GUIDing management of hypertension: The BP GUIDE study. *Am Heart J* 2012; 163: 761–767.
26. Sharman JE, Avolio AP, Baulmann J et al. Validation of non-invasive central blood pressure devices: ARTERY Society task force consensus statement on protocol standardization. *Eur Heart J* 2017; 38: 2805–2812.
27. Stergiou GS, Parati G, Vlachopoulos C et al. Methodology and technology for peripheral and central blood pressure and blood pressure variability measurement: Current status and future directions—Position statement of the European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability. *J Hypertens* 2016; 34: 1665–1677.
28. Vlachopoulos C, Aznaouridis K, O'Rourke MF et al. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: A systematic review and meta-analysis. *Eur Heart J* 2010; 31: 1865–1871.
29. Vlachopoulos C, Xaplanteris P, Aboyans V et al. The role of vascular biomarkers for primary and secondary prevention. A position statement from the European Society of Cardiology Working Group on Peripheral Circulation. *Atherosclerosis* 2015; 241: 507–532.
30. Weber T, Wassertheurer S, Schmidt-Trucksäss A et al. Relationship between 24-hour ambulatory central systolic blood pressure and left ventricular mass: A prospective multicenter study. *Hypertension* 2017; 70: 1157–1164.
31. Williams B, Lacy PS, Thom SM et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: Principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006; 113: 1213–1225.



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## INTRODUCTION

There is now international acceptance that ambulatory blood pressure measurement (ABPM) is the method of choice for diagnosing hypertension, for assessing the efficacy of management, and for making epidemiological outcome recommendations (1,2). The US Preventive Services Task Force (3), the UK National Institute for Health and Clinical Excellence (4), the European Society of Hypertension (2) and the Canadian Hypertension Education Program (5) have each carefully examined the evidence as to which method of blood pressure (BP) measurement is best, and have emphatically recommended ABPM as the method of choice. To add to this weight of international scientific opinion, the recently published American College of Cardiology and the American Heart Association (ACC/AHA) Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults has endorsed the use of ABPM in hypertension management, while recognizing that there will be considerable problems implementing its use in clinical practice (6,7,8).

These international bodies have recognized that using current strategies, clinicians have failed globally to reduce BP in hypertensive patients. Consequently, cardiovascular disease, for which hypertension is the main underlying cause, has been dubbed 'the largest epidemic ever known to mankind' (9). Indeed, at all ages, high BP is the major driver of cardiovascular complications (10). The Global Burden of Diseases Study 2010 reported that high BP is the leading risk factor for ill health and causes 9.4 million deaths every year – more than half of the estimated 17 million deaths per year attributable to total cardiovascular disease (11,12). This review summarizes the present status of ABPM.

## 24-HOUR AMBULATORY BLOOD PRESSURE MONITORING

Although ABPM has been available for over 30 years, its acceptance in clinical practice has been resisted for various reasons, and it remains much underused as the state-of-the-art technique for BP measurement (1,13). ABPM substantially refines the risk stratification provided by office

BP both in hypertensive patients (14–16) and in the general population (17–20). The greater number of readings, the absence of digit preference and observer bias, and the reduction of the white-coat effect all contribute to the predictive superiority of ambulatory over office BP (2).

Patients undergoing ABPM should keep a diary providing information on the awake and asleep periods, the intake of medications, the timing of meals and physical exercise and symptoms, if any. Short-fixed clock-time intervals that eliminate the transition periods in the morning and evening, during which BP changes rapidly, produce daytime and nighttime BP levels which are within 1–2 mmHg of the awake and asleep levels (21,22). Technological advances now allow devices for ABPM to indicate body position and activity, features that further enhance the relevance of the recorded BP. Innovative digital technologies are moving towards a cuffless approach to ABPM, thereby increasing patient comfort (23). However, none of these devices has been proven to generate data that predict adverse health outcomes or has received regulatory approval for out-of-office use. Table 24.1 lists the thresholds which have been recommended in guidelines to differentiate normotension from hypertension on daytime, nighttime and 24-hour ABPM. The International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcome (IDACO) includes randomly recruited population samples which had office and ABPM and cardiovascular risk factors measured at baseline with follow-up of fatal and nonfatal cardiovascular outcomes (24). In multivariable-adjusted analyses, we determined thresholds for ABPM, resulting in 10-year cardiovascular risk similar to those associated with optimal (120/80 mmHg), normal (130/85 mmHg) and high (140/90 mmHg) BP on in-office measurement (25). These outcome-driven thresholds are shown in Table 24.1.

As to the time of day that is most predictive of outcome, several studies in patients (14–16) or populations (17,18) have corroborated that nighttime compared with daytime BP is a better predictor of cardiovascular complications. In the IDACO database (19), nighttime BP adjusted for daytime BP predicted total, cardiovascular and noncardiovascular mortality. Conversely, adjusted for nighttime BP, daytime blood pressure predicted only noncardiovascular mortality, with lower BP levels being associated

**Table 24.1** Proposal for outcome-driven reference values for ambulatory blood pressure measurement

|                                | 24-Hour | Daytime | Nighttime |
|--------------------------------|---------|---------|-----------|
| Optimal blood pressure (mmHg)  | <115/75 | <120/80 | <100/65   |
| Normal blood pressure (mmHg)   | <125/75 | <130/85 | <110/70   |
| Ambulatory hypertension (mmHg) | ≥130/80 | ≥140/85 | ≥120/70   |

Source: Reproduced with permission from Kikuya M et al. *Circulation* 2007; 115: 2145–2152.

Note: Thresholds for the ambulatory blood pressure, resulting in 10-year cardiovascular risks similar to those associated with optimal (120/80 mmHg), normal (130/85 mmHg) or high (140/90 mmHg) blood pressure on office measurement.

with increased risk (19). Both daytime and nighttime BP predicted total cardiovascular events and stroke (19,20). Antihypertensive drug treatment removed the significant association between cardiovascular events and daytime BP (19). A subsequent IDACO publication clarified that isolated daytime hypertension and isolated nighttime hypertension both predicted adverse cardiovascular health outcomes (26). In addition to the minimization of confounding by antihypertensive drug treatment, usually taken in the morning or during the day, the standardized conditions during sleep (supine position and absence of movement) probably explain why the nighttime BP is the most accurate prognostic marker (14–19). This is in keeping with the concept originally enunciated by Smirk in 1964 that elevation of basal BP obtained following sedation was an accurate marker for adverse health outcomes (27).

The major contribution of ABPM to risk stratification is the cross-classification between office and ABPM in both untreated people or treated patients. In clinical practice, the commonly used definition of white-coat hypertension is a raised in-office BP in the presence of a normal daytime ABPM. Results of event-driven studies have convincingly demonstrated that the risk of cardiovascular disease is lower in patients with white-coat hypertension than in those with raised ABPM, even after controlling for concomitant risk factors (20). When daytime ABPM was below 130 mmHg systolic and 80 mmHg diastolic, the incidence of cardiovascular disorders did not differ between normotensive people and those with white-coat hypertension (26). The counterpart of white-coat hypertension is masked hypertension, a disorder characterized by a normal in-office BP confirmed at repeated clinic visits, but a raised daytime ABPM. Sustained hypertension refers to the joint elevation of both in-office and daytime BP. In the IDACO database, using a threshold of 135/85 mmHg, the prevalence of normotension and white-coat, masked and sustained hypertension was 49.4%, 10.6%, 14.5% and 25.5%, respectively. The multivariable-adjusted risk associated with white-coat hypertension did not differ from normotension, whereas masked hypertension conferred a risk approximating to that of sustained hypertension (Figure 24.1) (20).

In a further analysis of the IDACO database (1,28), we explored whether in untreated participants ABPM refines risk stratification. Among participants with office normotension (<120/<80 mmHg) or office pre-hypertension (120–139/80–89 mmHg), respectively, 198 (7.5%) and 900 (29.3%) had masked hypertension. Compared with true normotension, the multivariable-adjusted hazard ratios associated with masked hypertension in normotensive subjects were 2.11 ( $P = 0.007$ ) for a composite

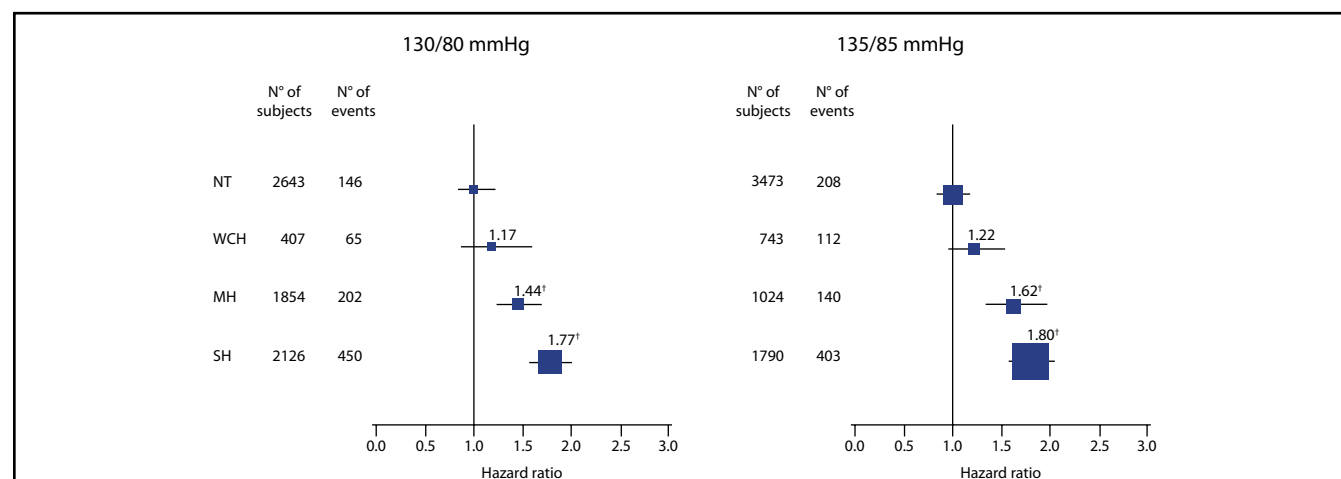


**Figure 24.1** Hazard ratios for cardiovascular events and stroke associated with masked hypertension on daytime blood pressure monitoring in participants with normotension or pre-hypertension. Participants with true normotension are the reference group. Normotension (<120/80 mmHg) and pre-hypertension (120–139/80–89 mmHg) refer to the classification based on the conventional blood pressure according to the JNC7/WHO-ISH criteria. Thresholds for daytime hypertension were ≥135 mmHg systolic or ≥85 mmHg diastolic. The hazard ratios were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications and diabetes mellitus. Horizontal lines denote the 95% confidence interval. Compared to pre-hypertension without masked hypertension, the hazard ratios associated with masked hypertension in prehypertensive subjects were 1.53 (95% confidence interval [CI], 1.23–1.91;  $P = 0.0001$ ) for the composite cardiovascular endpoint and 1.48 (CI, 1.01–2.16;  $P = 0.04$ ) for stroke. (Reproduced with permission from the study of Brguljan-Hitij J et al. *Am J Hypertens* 2014; 27: 956–965.)

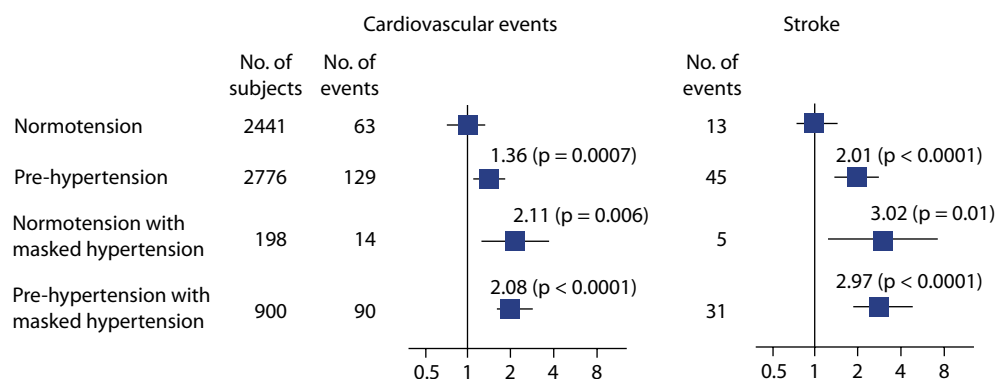


**Figure 24.2** Hazard ratios associated with masked hypertension ( $\geq 135/85$  mmHg) on home blood pressure monitoring in participants with optimal, normal or high-normal office blood pressure. Participants with optimal blood pressure without elevated home blood pressure were the reference group. Systolic/diastolic thresholds for the conventional blood pressure were optimal ( $<120/80$  mmHg), normal ( $120\text{--}129/80\text{--}84$  mmHg), and high-normal ( $130\text{--}139/85\text{--}89$  mmHg). When a systolic or diastolic blood pressure was in a different category, the participant was assigned to the higher category. Systolic/diastolic thresholds for hypertension on home measurement were  $\geq 135/85$  mmHg. MHT indicates masked hypertension. The hazard ratios were adjusted for cohort, sex, age, body mass index, smoking, total cholesterol, diabetes mellitus, and history of cardiovascular disease. Horizontal lines denote the 95% confidence interval. MHT indicates masked hypertension. The diamond represents the pooled estimate in all patients with MHT. The P value for heterogeneity was derived by testing an ordinal variable in Cox proportional hazard regression coding for the three subgroups among patients with MHT. (Reproduced with permission from the study of Asayama K et al. *PLOS MED* 2014; 11: e1001591 (47).)

cardiovascular endpoint and 3.02 ( $P = 0.01$ ) for stroke (Figure 24.2) (28). The corresponding hazard ratios associated with masked hypertension in prehypertensive subjects were 2.08 ( $P < 0.0001$ ) and 2.97 ( $P < 0.0001$ ), respectively. Compared to pre-hypertension without masked hypertension, the hazard ratios associated with masked hypertension in prehypertensive subjects were 1.53 ( $P = 0.0001$ ) for the composite cardiovascular endpoint and 1.48 ( $P = 0.04$ ) for stroke (Figure 24.2) (28). These findings remained consistent, if masked hypertension was based on the 24-hour or nighttime BP (28). ABPM also enhances risk stratification in apparently normotensive people with optimal, normal or high-normal office BP, and who present with diabetes (29).

The probability of having masked hypertension increases with an office BP in the normal or high-normal range (odds ratio [OR] 5.1 vs. optimal office blood pressure), age 40 years or older (OR 2.5 vs. being younger than 40 years), overweight or obesity (OR 2.0), alcohol intake (OR 1.9), diabetes mellitus (OR 1.8) and smoking (OR 1.5). Other risk factors include a family history of hypertension in both parents, patients with multiple risk factors for cardiovascular disease, male sex and higher awake heart rate (30).

An issue of clinical importance is whether self-monitoring of BP at home can replace ABPM as the gold standard of out-of-office blood pressure measurement. The answer is negative. First, home BP measurement does not allow easy recording of nocturnal BP, the window of the day during which BP is most predictive of adverse cardiovascular outcome (14–20). Second, isolated nocturnal hypertension has a prevalence of 7% among Caucasians (26,31) and of 10–11% among blacks (32) and Asians (26,31,32), and confers a risk equal to that of an elevated daytime BP (33). Only 24-hour ABPM makes diagnosing isolated nocturnal hypertension straightforward. Third, ABPM is the

preferred method for diagnosing hypotension, particularly in seniors, in whom postprandial and postural hypotension are common because of impairment of the autonomic nervous system and an attenuated baroreceptor reflex. The diagnosis of symptomatic drug-induced hypotension is a key issue in patients who have a compromised arterial circulation, such as those with coronary and cerebrovascular disease, and fragile elderly patients (13). Fourth, whereas carotid atherosclerosis was associated with the home BP in Japanese, ABPM in the same cohort was a stronger predictor of silent cerebrovascular disease (34). Finally and foremost, using home instead of ABPM misses the high-risk diagnoses of masked or sustained hypertension in over 25% of patients (35). Indeed, in 831 untreated outpatients (mean age, 50.6 years; 49.8% women), we measured office (three visits), home (7 days), and 24-hour ABPM. We applied hypertension guidelines for the cross-classification of patients into normotension or white-coat, masked or sustained hypertension (Table 24.1). Based on office and home BP, the number (percentage) of patients with white-coat, masked and sustained hypertension was 61 (10.3%), 166 (20.0%) and 162 (19.5%), respectively. Using daytime instead of home BP confirmed the cross-classification in 575 patients (69.2%), downgraded risk from masked hypertension to normotension ( $n = 24$ ) or from sustained to white-coat hypertension ( $n = 9$ ) in 33 patients (4.0%), but upgraded the risk from normotension to masked hypertension ( $n = 179$ ) or from white-coat to sustained hypertension ( $n = 44$ ) in 223 (26.8%) (35). Analyses based on the 24-hour instead of the daytime ABPM were confirmatory. In adjusted analyses, both the urinary albumin-to-creatinine ratio ( $+20.6\%$ ; CI 4.4–39.3) and aortic pulse wave velocity ( $+0.30$  m/s; CI 0.09–0.51) were higher in patients who moved up to a higher risk category (35). Both indices of target-organ damage as well as the central augmentation index were positively associated

( $P \leq 0.048$ ) with the odds of being reclassified to a higher risk category (35).

## AMBULATORY MONITORING AS TREATMENT GUIDE

The European Society of Hypertension position paper, although giving considerable attention to the diagnostic role of ABPM, has relatively little to say on the use of this technique for initiating and following the efficacy of treatment (2). This omission becomes particularly important in the context of the suboptimal BP control rates, largely based on in-office BP measurement, common to so many countries. The largest study to date on ABPM in primary care comes from Spain, where a nationwide project to promote the use of this technique in primary care settings was established a decade ago (36). The concluding messages from the Spanish study were that, compared to casual BP measurement, ABPM led to a reduction in the proportion of older subjects recommended for hypertension treatment and a substantial increase in the proportion of those whose hypertension was controlled (36).

## INITIATION OF TREATMENT

The guidelines are unanimous in recommending ABPM in all patients under consideration for BP-lowering medication (2–8). The rationale behind these recommendations is basically to confirm that the elevation of BP is sustained on out-of-office measurement and not due to a white-coat reaction, as may occur in 25% of patients (37).

## ASSESSING INITIAL TREATMENT EFFICACY

International guidelines have not as yet made definitive recommendations as to how ABPM should be used in assessing the efficacy of prescribed treatment. Regardless of the patient's risk factor profile, the aim of all treatment strategies should be the restoration of BP to normal throughout the 24-hour period. Of course, if the risk factor profile of the patient is bad, for instance because of target-organ damage, a history of cardiovascular disease or comorbidities, such as diabetes, the need to reduce BP becomes more pressing. So, having initiated treatment (and it is not within the scope of this review to discuss how this might be done), it would seem reasonable to repeat ABPM within 3–6 weeks to determine if adequate BP reduction has been achieved. If further adjustments in therapy are required, as may often be the case, then repeating ABPM at 3- to 6-week intervals until control is achieved is justifiable. There is, however, another aspect of treatment that merits consideration; namely, excessive lowering of BP, especially of the nocturnal pressure. Excessive elevation of nocturnal BP entails cardiovascular risk, but a group of patients may be adversely affected by excessive lowering of the BP at night (38). Up-titration of treatment based on the office BP must be done without knowing the status of nocturnal hypotension.

## ASSESSING LONG-TERM EFFICACY

Once 24-hour control of BP has been achieved, ABPM need only be repeated at 6-monthly or annual intervals. Self-measurement of BP at home can be used to obtain confirmatory evidence that BP control is being maintained, at least for the daytime BP (39,40). However, to obtain a self-measured BP equivalent to the daytime ABPM, 6 days of measurement are required – two readings in the morning and two in the evening, after discarding the measurements from the first day. Many patients and doctors consider this as being more onerous than performing ABPM which, in addition, provides the nocturnal BP, the best predictor of outcome (14–19,32).

## CLINICAL IMPLEMENTATION

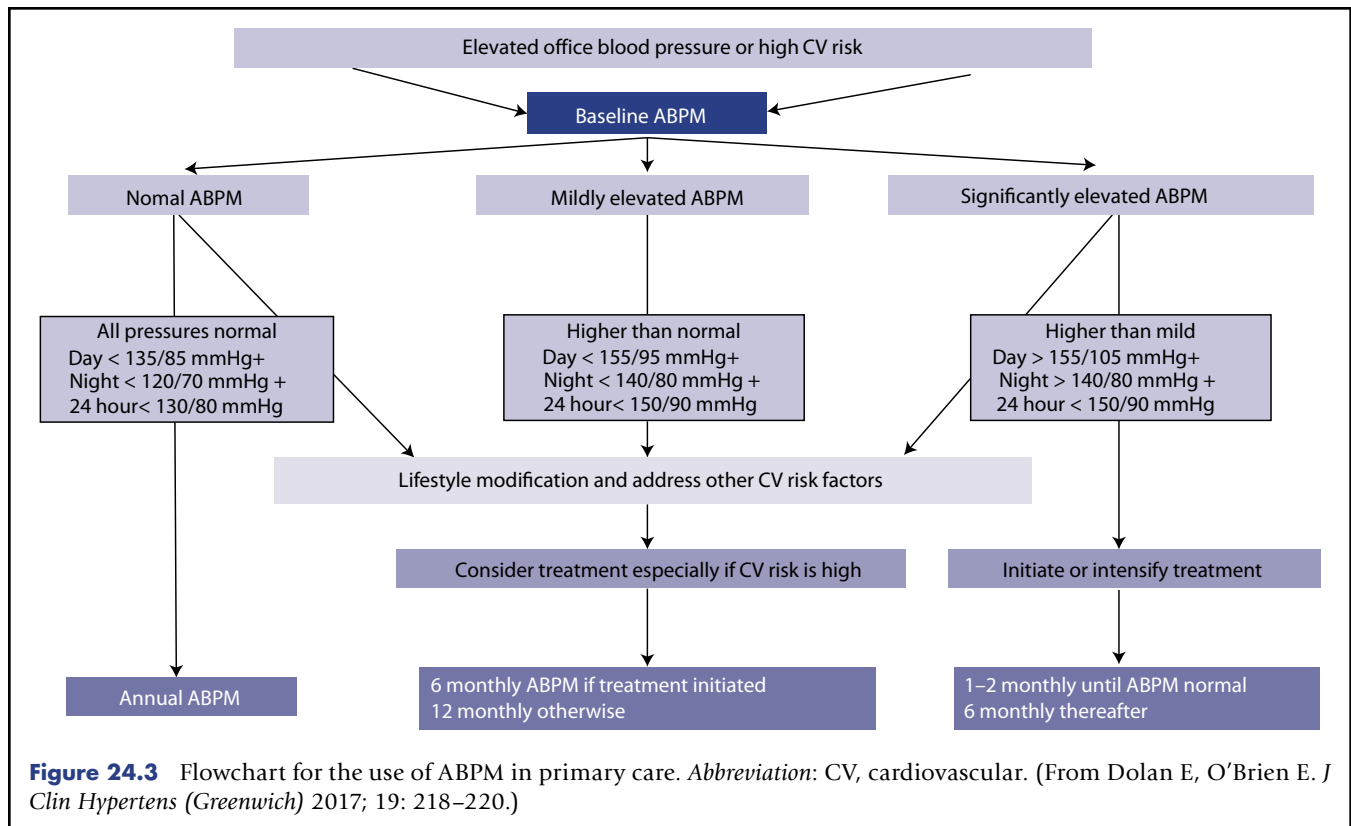
The most advantageous development in BP measurement would be for manufacturers to produce an accurate, inexpensive, user-friendly and versatile 'device for all seasons' that would allow doctors, pharmacists and patients to measure office, home and ambulatory BP, according to the indication, with the means for appropriate transmission, storage and analysis of the data.

The schema put forward in Figure 24.3 might serve as a guide for the use of ABPM in clinical practice (41).

To be equitable, health insurance should provide easy access to the diagnostic procedures that allow risk stratification based on BP and the rational use of antihypertensive drugs. Failure to provide adequate reimbursement for ABPM is mitigating against implementation of the international recommendations (2–8). From a European perspective, ABPM is not reimbursed in Belgium, Denmark, France and Spain. The National Health Service in the United Kingdom provides free access to healthcare, including ABPM. In Ireland (€60 per recording in general practice), Norway (€40 per recording in primary and specialized care) and Finland (free of cost or €60 per recording in public and private healthcare, respectively) ABPM is covered by health insurance. In Ireland, pharmacies contribute to making ABPM more accessible at a cost for patients varying from €40 to €100 per recording. Self-measurement of BP is not reimbursed in any of the aforementioned countries except in Denmark, where home BP measurement is reimbursed on condition that hypertension is likely to be present based on office BP readings at two or more visits, and when there is resistant hypertension or large variability in the office BP readings. In China, ABPM is covered by health insurance at a cost varying from €12 to €45 per recording in both primary and referral hospitals, but home BP monitoring is not reimbursed.

Several studies have addressed the cost-effectiveness of ABPM. It was thought originally that the main financial benefit of ABPM would be a reduction in the healthcare costs due to avoiding antihypertensive drug treatment in white-coat hypertensive patients (42–44). However, Krakoff has shown that the cost savings with ABPM in newly detected hypertensive patients should include the savings from not only treatment savings but also the benefits of treatment in the prevention of the complications of hypertension. His analyses indicated potential savings of 3–14% for the cost of care for hypertension and a 10–23% reduction in treatment days when ABPM is incorporated into the diagnostic process (45).





In 2011, Lovibond et al. published a Markov model–based probabilistic cost-effectiveness analysis which showed that in a hypothetical primary care population aged 40 years or older with screening BP measurements greater than 140 mmHg systolic and 90 mmHg diastolic and a risk factor prevalence representative for the general population, ABPM was the most cost-effective strategy for the diagnosis of hypertension for women and men of all ages and resulted in more quality of life–adjusted life years for women and for men older than 50 years. To our knowledge, none of the published cost-benefit estimates accounted for the 15% prevalence of masked hypertension in the general population and the associated adverse health outcomes that equal those of sustained hypertension (46).

## CONCLUSIONS

The take-home message of this review is that ABPM is the state-of-the-art technique of BP measurement and is indispensable for the diagnosis of hypertension and for the decision to initiate or adjust antihypertensive drug treatment. In an era in which the cost for the equipment required for ABPM is decreasing, healthcare providers should facilitate a generalized access to this state-of-the-art technology without limitations in terms of the frequency of the recordings.

Manufacturers might support this effort by designing versatile devices that can be used for all types of BP measurement and by considering market size rather than profit margins per single device sold. The only provision on which one should never compromise is that physicians

and nurses, be it in primary or specialized care, have to prove that they have acquired the skills necessary for understanding the principles of BP measurement, cuff fitting, monitor function and analysis and interpretation of ABPM recordings.

## REFERENCES

1. Staessen JA, Li Y, Hara A, Asayama K et al. Blood pressure measurement anno 2016. *Am J Hypertens* 2017; 30: 453–463.
2. O'Brien E, Parati G, Stergiou G et al. European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens* 2013; 31: 1731–1768.
3. Siu AL; U.S. Preventive Services Task Force. Screening for high blood pressure in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2015; 163: 778–786.
4. National Institute for Health and Clinical Excellence (NICE). *The Clinical Management of Primary Hypertension in Adults*. National Institute for Health and Clinical Excellence, London, UK; 2011.
5. Leung AA, Nerenberg K, Daskalopoulou SS et al. CHEP Guidelines Task Force. Hypertension Canada's 2016 Canadian hypertension education program guidelines for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol* 2016; 32: 569–588.
6. Whelton PK, Carey RM, Aronow WS et al. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/ NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2017 [published online November 13, 2017]. doi: [10.1161/HYP.0000000000000065](https://doi.org/10.1161/HYP.0000000000000065).
7. Whelton PK, Carey RM, Aronow WS et al. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/ NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017 [published online November 13, 2017]. doi: [10.1016/j.jacc.2017.11.006](https://doi.org/10.1016/j.jacc.2017.11.006).



8. Greenland P, Peterson E. The new 2017 ACC/AHA guidelines 'Up the Pressure' on diagnosis and treatment of hypertension. *JAMA* 2017; 318(21): 2083–2084; On-line.
9. Yusuf S, Wood D, Ralston J, Reddy KS. The World Heart Federation's vision for worldwide cardiovascular disease prevention. *Lancet* 2015; 386: 399–402.
10. Lewington S, Clarke R, Qizilbash N et al. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360: 1903–1913.
11. Lim SS, Vos T, Flaxman AD et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2224–2260.
12. Murray CJ, Ezzati M, Flaxman AD et al. GBD 2010: Design, definitions, and metrics. *Lancet* 2012; 380: 2063–2066.
13. O'Brien E, Stergiou GS. The pursuit of accurate blood pressure measurement: A 35-year Travail. *J Clin Hypertens (Greenwich)* 2017; 19: 746–752.
14. Verdecchia P, Porcellati C, Schillaci G et al. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension* 1994; 24: 793–801.
15. Staessen JA, Thijs L, Fagard R et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA* 1999; 282: 539–546.
16. Clement DL, De Buyzere ML, De Bacquer DA et al. Office versus Ambulatory Pressure Study Investigators. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med* 2003; 348: 2407–2415.
17. Dolan E, Stanton A, Thijs L et al. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: The Dublin Outcome Study. *Hypertension* 2005; 46: 156–161.
18. Ben-Dov IZ, Kark JD, Ben-Ishay D et al. Predictors of all-cause mortality in clinical ambulatory monitoring: Unique aspects of blood pressure during sleep. *Hypertension* 2007; 49: 1235–1241.
19. Boggia J, Thijs L, Hansen TW et al. International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO) investigators. Prognostic accuracy of day versus night ambulatory blood pressure: A cohort study. *Lancet* 2007; 370: 1219–1229.
20. Hansen TW, Kikuya M, Thijs L et al. Prognostic superiority of daytime ambulatory over conventional blood pressure in four populations: A meta-analysis of 7,030 individuals. *J Hypertens* 2007; 25: 1554–1564.
21. Li Y, Kikuya M, Thijs L et al. Are published characteristics of the ambulatory blood pressure generalizable to rural Chinese? The JingNing population study. *Blood Press Monit* 2005; 10: 125–134.
22. Fagard R, Brguljan J, Thijs L, Staessen J. Prediction of the actual awake and asleep blood pressures by various methods of 24 h pressure analysis. *J Hypertens* 1996; 14: 557–563.
23. Steinhubl SR, Muse ED, Barrett PM, Topol EJ. Off the cuff: Rebooting blood pressure treatment. *Lancet* 2016; 388: 749–750.
24. Thijs L, Hansen TW, Kikuya M et al. The International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcome (IDACO): Protocol and research perspectives. *Blood Press Monit* 2007; 12: 255–262.
25. Kikuya M, Hansen TW, Thijs L et al. International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes Investigators. Diagnostic thresholds for ambulatory blood pressure monitoring based on 10-year cardiovascular risk. *Circulation* 2007; 115: 2145–2152.
26. Fan HQ, Li Y, Thijs L et al. International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes Investigators. Prognostic value of isolated nocturnal hypertension on ambulatory measurement in 8711 individuals from 10 populations. *J Hypertens* 2010; 28: 2036–2045.
27. Smirk FH. Observations on mortality of 270 treated and 199 untreated retinal grade I and II hypertensive patients followed in all instances for 5 years. *N Z Med J* 1964; 63: 413–443.
28. Brguljan-Hitij J, Thijs L, Li Y et al. International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome Investigators. Risk stratification by ambulatory blood pressure monitoring across JNC classes of conventional blood pressure. *Am J Hypertens* 2014; 27: 956–965.
29. Franklin SS, Thijs L, Li Y et al. International Database on Ambulatory blood pressure in Relation to Cardiovascular Outcomes Investigators. Masked hypertension in diabetes mellitus: Treatment implications for clinical practice. *Hypertension* 2013; 61: 964–971.
30. Fagard RH, Stolarz K, Kuznetsova T et al. Sympathetic activity, assessed by power spectral analysis of heart rate variability, in white-coat, masked and sustained hypertension versus true normotension. *J Hypertens* 2007; 25: 2280–2285.
31. Staessen JA, O'Brien ET, Amery AK et al. Ambulatory blood pressure in normotensive and hypertensive subjects: Results from an international database. *J Hypertens* 1994; 12(Suppl. 7): S1–S12.
32. Li Y, Staessen JA, Lu L et al. Is isolated nocturnal hypertension a new clinical entity? *Hypertension* 2007; 50: 333–339.
33. O'Brien E, Asmar R, Beilin L et al. European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003; 21: 821–848.
34. Hara A, Tanaka K, Ohkubo T et al. Ambulatory versus home versus clinic blood pressure: The association with subclinical cerebrovascular diseases: The Ohasama Study. *Hypertension* 2012; 59: 22–28.
35. Zhang L, Li Y, Wei FF et al. Strategies for classifying patients based on office, home, and ambulatory blood pressure measurement. *Hypertension* 2015; 65: 1258–1265.
36. Banegas JR, de la Cruz JJ, Graciani A et al. Impact of ambulatory blood pressure monitoring on reclassification of hypertension prevalence and control in older people in Spain. *J Clin Hypertens (Greenwich)* 2015; 17: 453–461.
37. Pickering TG, James GD, Boddie C et al. How common is white coat hypertension? *JAMA* 1988; 259: 225–228.
38. Dolan E, Stanton AV, Thom S et al. Ambulatory blood pressure monitoring predicts cardiovascular events in treated hypertensive patients—an Anglo-Scandinavian cardiac outcomes trial substudy. *J Hypertens* 2009; 27: 876–885.
39. Sheppard JP, Stevens R, Gill P et al. Predicting Out-of-Office Blood Pressure in the Clinic (PROOF-BP): Derivation and validation of a tool to improve the accuracy of blood pressure measurement in clinical practice. *Hypertension* 2016; 67: 941–950.
40. Wei FF, Li Y, Zhang L et al. Persistence of masked hypertension in Chinese patients. *Am J Hypertens* 2016; 29: 326–331.
41. Dolan E, O'Brien E. How should ambulatory blood pressure measurement be used in general practice? *J Clin Hypertens (Greenwich)* 2017; 19: 218–220.
42. Staessen JA, Byttebier G, Buntinx F et al. Antihypertensive treatment based on conventional or ambulatory blood pressure measurement. A randomized controlled trial. Ambulatory Blood Pressure Monitoring and Treatment of Hypertension Investigators. *JAMA* 1997; 278: 1065–1072.
43. Staessen JA, Den Hond E, Celis H et al. Antihypertensive treatment based on blood pressure measurement at home or in the physician's office: A randomized controlled trial. *JAMA* 2004; 291: 955–964.
44. Verberk WJ, Kroon AA, Lenders JW et al. Home Versus Office Measurement, Reduction of Unnecessary Treatment Study Investigators. Self-measurement of blood pressure at home reduces the need for antihypertensive drugs: A randomized, controlled trial. *Hypertension* 2007; 50: 1019–1025.
45. Krakoff LR. Cost-effectiveness of ambulatory blood pressure: A reanalysis. *Hypertension* 2006; 47: 29–34.
46. Lovibond K, Jowett S, Barton P et al. Cost-effectiveness of options for the diagnosis of high blood pressure in primary care: A modelling study. *Lancet* 2011; 378: 1219–1230.
47. Asayama K, Thijs L, Brguljan-Hitij J et al. Risk stratification by self-measured home blood pressure across categories of conventional blood pressure: A participant-level meta-analysis. *PLOS MED* 2014; 11: e1001591.

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## INTRODUCTION

In the last decades blood pressure (BP) monitoring out of the office using self-monitoring by patients at home (HBPM), or 24-hour ambulatory BP monitoring (ABPM), has gained a central role in hypertension diagnosis and management (1–7). Out-of-office BP monitoring allows the detection of the white-coat and masked hypertension phenomena, which are common among both untreated and treated subjects, and has superior cardiovascular prognostic value than the conventional office BP (OBP) measurements (1–7). Thus, HBPM is endorsed by both European and US guidelines for hypertension diagnosis and management (1–4). HBPM is widely available and accepted by patients, and has several advantages but also some limitations (Table 25.1) (5,6).

## DIAGNOSTIC VALUE

Several cross-sectional studies have investigated the diagnostic performance of HBPM, usually by taking ABPM as a reference method. Despite the large heterogeneity in their design (selected diagnostic phenotypes of hypertension, subjects' characteristics, treatment status, comorbidities, etc.), these studies suggest considerable diagnostic agreement between HBPM and ABPM ranging from about 70 to 90%, with consistently high specificity and negative predictive value (>80%) and lower sensitivity and positive predictive value (60–70%) (8). However, these findings should be interpreted with some caution since: (i) both ABPM (used as reference) and HBPM have imperfect reproducibility (which contributes to their diagnostic disagreement), and (ii) the diagnostic disagreement between the two methods is more prominent in subjects with BP levels close to the diagnostic thresholds, leading to 'arithmetical' discrepancy which is usually not clinically relevant (8,9). Moreover, HBPM provides BP readings under standardized conditions (only in the sitting posture at home) and therefore it does not represent the dynamic behaviour of BP during usual daily activities (5,6). In addition, it has been shown that the relationship between OBP, HBPM and ABPM is not the same across all age groups, which

should be taken into account when examining their diagnostic agreement (10).

## PROGNOSTIC VALUE

Two meta-analyses evaluated the association of HBPM with preclinical target-organ damage (11,12). The first examined the association of HBPM versus OBP and ABPM with indices of organ damage (11). Most of the evidence was based on echocardiographic left ventricular mass index, and analysis of 10 studies revealed stronger correlation coefficients for HBPM than OBP (11). In addition, data from nine studies indicated similar coefficients for HBPM and ABPM (11). The evidence is weaker for carotid intima-media thickness, pulse wave velocity and urine protein excretion, with a consistent trend towards stronger coefficients for HBPM than OBP, with the latter not reaching statistical significance (11). The second meta-analysis, which included more trials, suggested that HBPM is a stronger determinant of proteinuria than OBP (12).

The abovementioned superiority of HBPM over OBP in terms of cardiovascular risk is complemented and further supported by prospective outcome studies. Two meta-analyses based on aggregate data from eight prospective studies and 17,688 patients (general population, primary care and hypertensive patients) followed for 3.2–10.9 years showed HBPM to be a significant predictor of cardiovascular mortality and cardiovascular events after adjusting for OBP (13,14). The International Database of Home blood pressure in relation to Cardiovascular Outcome (IDHOCO) was constructed using individual participants' data of published population studies and evaluated the prognostic value of HBPM (n = 6458, mean follow-up 8.3 years) (15). In this analysis, masked hypertension (low OBP and elevated HBPM) was associated with increased cardiovascular risk in both untreated and treated subjects (masked uncontrolled hypertension) (15). Moreover, white-coat hypertension (elevated OBP, normal HBPM) was associated with increased cardiovascular risk in untreated but not in treated subjects (15). Thus, HBPM appears to have independent prognostic value and allows more accurate risk stratification than

**Table 25.1** Advantages and limitations of home blood pressure monitoring

| Advantages                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Limitations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>■ Large number of self-blood pressure measurements taken in the individual's usual environment.</li> <li>■ More reproducible BP values than with office measurements.</li> <li>■ Detection of white-coat and masked hypertension phenomena in both untreated and treated subjects.</li> <li>■ Devoid of placebo effect.</li> <li>■ Closer association with preclinical organ damage than with office BP measurements.</li> <li>■ Better prediction of cardiovascular events than with office BP measurements.</li> <li>■ Devoid of observer error, prejudice and bias with automated electronic devices.</li> <li>■ Devoid of reporting bias of self-BP measurements by patients with electronic devices with automated memory, PC link or telemonitoring function.</li> <li>■ Improves long-term patient compliance with drug treatment.</li> <li>■ Improves hypertension control rates.</li> <li>■ Wide availability in most countries.</li> <li>■ Need of minimal training (with automated devices).</li> <li>■ Good acceptance by hypertensive patients for long-term use.</li> <li>■ Cost-effective.</li> </ul> | <ul style="list-style-type: none"> <li>■ Most devices available on the market have not been validated for accuracy using an established protocol.</li> <li>■ Misreporting (over- or under-) of BP readings by some patients.</li> <li>■ Need of user training (minimal with automated devices) and medical supervision.</li> <li>■ May induce anxiety and too frequent monitoring in some patients.</li> <li>■ Some patients may self-modify their drug treatment on the basis of casual BP readings.</li> <li>■ Measurements performed under standardized conditions (sitting at home) do not reflect usual daily activities.</li> <li>■ Inability to monitor BP during nighttime sleep (possible with some novel home monitors).</li> <li>■ Questionable accuracy of automated oscillometric devices in the presence of arrhythmias.</li> </ul> |

OBP, particularly in cases with masked hypertension. Additional analyses of the IDHOCO database showed home day-to-day BP variability to independently predict cardiovascular outcome (16).

## ROLE IN MANAGEMENT OF HYPERTENSION

Because of its diagnostic accuracy and prognostic value, HBPM has a crucial role in the long-term management of hypertension. This method motivates the patients by increasing their awareness and rendering them actively involved in their own monitoring and long-term follow-up. Several randomized controlled trials have shown that treated hypertensives who perform HBPM have improved long-term adherence to drug therapy, and thereby improved hypertension control rates (17,18).

Two prospective studies compared HBPM versus ABPM for treatment adjustment (19,20). The first, in 98 subjects followed for 6 months, found no difference in BP control when using HBPM or ABPM (19). The second randomized 116 subjects to treatment initiation and titration based either on HBPM alone or on combined use of OBP and ABPM (20). After a follow-up of 13.4 months, there was no difference between the two arms in BP decline and hypertension control assessed by HBPM or ABPM and, more importantly, there was no difference in treatment-induced changes in several indices of preclinical target-organ damage (20).

## TECHNOLOGY AND METHODOLOGY

With the progress of technology and methodology, attention has been recently focused on innovative roles of HBPM, such as tele-HBPM, atrial fibrillation (AF) detection and nighttime HBPM.

Tele-HBPM is based on registration of BP data obtained by the patient at home and their transmission to a remote

computer through telephone or internet connection. Several studies suggest that tele-HBPM allows more reliable and objective evaluation and is associated with higher BP control rates and increased patient satisfaction, especially when accompanied with counselling support from study personnel; however, its wide applicability and cost-effectiveness require further research (21,22).

Automated BP measurement using the oscillometric method in AF faces several difficulties (23). However, the available evidence suggests that the oscillometric method is feasible and appears to be accurate, at least for systolic BP measurement, which is more important for AF patients, who are almost exclusively elderly (24). Screening for AF with automated BP measurement is an attractive strategy in the context of the guideline-recommended opportunistic screening. A specific algorithm for AF detection during automated BP measurement has been developed and implemented in a novel oscillometric home BP monitor (Microlife WatchBP Home-A) with satisfactory diagnostic accuracy (25). In 2013, the UK National Institute for Health and Care Excellence recommended this device for AF screening in subjects  $\geq 65$  years (26).

Accumulating evidence suggests that nighttime BP, assessed by ABPM, is the most important aspect of the BP profile in terms of prognosis (7). During the last decade, novel low-cost HBPM devices that allow automated nighttime BP monitoring have been developed. A recent meta-analysis of six studies showed that nighttime HBPM is feasible, and compared to nighttime ABPM it presents similar BP values, has satisfactory agreement in detecting non-dippers and has a comparable relationship with target-organ damage (27).

## HOME VERSUS OFFICE AND AMBULATORY BLOOD PRESSURE MONITORING

Both HBPM and ABPM provide multiple measurements in the usual environment of each individual, allowing more

accurate assessment of the BP profile compared to OBP. However, HBPM is performed under standardized conditions (only in the sitting posture and at home), whereas ABPM is performed in fully ambulatory conditions and posture (at home, work or during sleep, without a period of sitting rest before each measurement) (5–7). Despite these differences, average HBPM and daytime ABPM appear to have similar normalcy thresholds, similar reproducibility, similar diagnostic accuracy for white-coat and masked hypertension and similar prognostic value, with all these features being superior to those of the conventional OBP measurements (1–7).

The similarity between HBPM and ABPM does not mean that the two methods are interchangeable. This was clearly demonstrated in two population outcome studies (PAMELA, Ohasama) where subjects with elevated ambulatory but low home BP or the reverse were at increased cardiovascular risk compared to normotensives (low home and ambulatory BP), implying independent prognostic information was provided by each method (28,29). Thus, these methods should be regarded as complementary rather than competitive in the assessment of hypertensive patients. The 2017 US guidelines recommend HBPM or ABPM to be used for the detection of white-coat and masked hypertension in untreated patients, whereas HBPM has a primary role of detecting these phenomena in treated patients (confirmation with ABPM is needed in masked uncontrolled hypertension detected by HBPM) (4). The advantages and differences between BP monitoring methods are presented in Table 25.2.

## CLINICAL APPLICATION AND RECOMMENDATIONS (TABLE 25.3)

### CLINICAL INDICATIONS

The main clinical indications for HBPM include confirmation of hypertension diagnosis, detection of white-coat and masked hypertension, identification of white-coat reaction and masked hypertension effect in treated hypertensives, overcoming considerable variability of OBP over the same or different visits, identification of true and false resistant hypertension, titration of BP-lowering medication and assessment of long-term BP control in treated hypertension (1–4).

### DEVICES

Validated automated electronic devices, especially those using an oscillometric algorithm and having an upper-arm cuff, are currently recommended for HBPM, as they are relatively accurate, user friendly, relatively cheap, devoid of observer bias and require little training (1–4). The accuracy of electronic BP monitors should be tested against conventional sphygmomanometry according to established validation protocols (30–33). Unfortunately, most of the electronic BP monitors available on the market have not been subjected to independent validation for their measurement accuracy. Aneroid or hybrid auscultatory devices can also be used but require observer skills,

**Table 25.2** Comparison of the features of office, ambulatory and home blood pressure measurements

| BP method feature                          | Office | Ambulatory | Home |
|--------------------------------------------|--------|------------|------|
| Detection of white-coat hypertension       | –      | ++         | ++   |
| Detection of masked hypertension           | –      | ++         | ++   |
| Assessment of nighttime BP level and dip   | –      | ++         | +    |
| Assessment of morning BP surge             | –      | ++         | –    |
| Assessment of morning hypertension         | +/–    | ++         | ++   |
| Assessment of antihypertensive drug action | +      | ++         | ++   |
| Assessment of duration of drug action      | +/–    | ++         | +    |
| Long-term follow-up of hypertension        | ++     | +/–        | ++   |
| Improvement of patients' compliance        | +      | –          | ++   |
| Improvement of hypertension control rate   | +      | –          | ++   |
| Reproducibility                            | –      | ++         | ++   |
| Prognostic value                           | +      | ++         | ++   |
| Availability                               | ++     | –          | ++   |
| Cost                                       | –      | –          | ++   |

training and more regular calibration, which usually are not feasible in general practice. Some automated wrist devices have passed the internationally accepted validation protocols; however, these are regarded as less accurate than upper-arm devices, mainly because of anatomical differentiations of the wrist, and difficulty in following the correct wrist position (at heart level and relaxed) (1–4). Updated lists of devices which have passed official validation protocols are available at several websites ([www.bhsoc.org](http://www.bhsoc.org); [www.medaval.org](http://www.medaval.org); [www.dablededucational.org](http://www.dablededucational.org)).

The use of a cuff with appropriate inflatable bladder size for the arm circumference of each individual is of equal importance as the accuracy of the device (1–4). As a general rule, the length of the inflatable bladder should cover 75–100% of the arm circumference and the width should be about half of the length, yet some oscillometric devices might give accurate measurements with a smaller cuff (1). Cuffs which are too small for the arm circumference tend to overestimate BP (common in obese subjects), whereas cuffs which are too large (in children or lean subjects) tend to underestimate BP. It is generally recommended that subjects with arm circumference larger than 32 cm should use a cuff larger than the standard size, while those with arm circumference smaller than 24 cm should use a smaller cuff than the standard (1).



**Table 25.3** Recommendations for practical application of self-home blood pressure monitoring

|                      |                                                                                                                                                                                                  |
|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Device               | Automated upper-arm cuff electronic (oscillometric) device which has been validated according to an established protocol.                                                                        |
| Cuff size            | Bladder size to fit the individual's arm circumference.                                                                                                                                          |
| Conditions           | Relaxed and after 5 min sitting rest. Back supported, arm relaxed and supported with middle of upper arm at heart level, legs uncrossed, feet flat on the floor. No talking during measurements. |
| Monitoring schedule  | 7-day monitoring before each visit to the doctor, with duplicate morning and evening measurements (before drug intake). Not less than 3 days monitoring and less than 12 readings.               |
| Evaluation           | Calculation of average BP of all readings (at least 8 after discarding readings of the first day). Casual BP readings have little clinical relevance.                                            |
| Interpretation       | Home hypertension: $\geq 135/85$ mmHg; Normal home BP: $<130/80$ mmHg; Home BP $130\text{--}135/80\text{--}85$ mmHg to be considered as borderline.                                              |
| Long-term monitoring | 1–2 duplicate measurements per week. Too frequent monitoring (e.g. every day) and self-modification of treatment on the basis of casual measurements to be avoided.                              |

Source: Reprinted from *Hypertension: A Companion to Braunwald's Heart Disease*, 3rd edn., Stergiou GS, Kollias A, Home monitoring of blood pressure, 89–95, Copyright 2018, with permission from Elsevier.

## MONITORING CONDITIONS, PROCEDURE AND SCHEDULE

The conditions of HBPM should be similar to those recommended for OBP (1–4). The patient should be relaxed in the sitting posture, with the back supported, with legs uncrossed and feet flat on the floor, in a quiet room at a comfortable temperature, and at least 5 min of rest should precede the measurement (1–4). The subject should avoid smoking, caffeinated beverages, or exercise within 30 min before BP measurements, and talking during the resting period and the BP measurements should be discouraged (1–4). The cuff should be placed at heart level with the centre of the bladder over the brachial artery and the bottom of the cuff directly above the antecubital fossa (1–4).

Regarding the monitoring schedule, current European and US guidelines recommend a standard HBPM schedule for the initial evaluation of BP levels (untreated subjects), after any change in the treatment regimen, and also before any routine visit to the doctor (for treated hypertensives), which includes duplicate measurements (with 1 minute interval) in the morning (before drug intake if treated), and the evening, for 7 routine workdays (not less than 3 days), with weekends preferably excluded, as the corresponding BP values are usually lower than in workdays

(1–4,34). For decision making, a total of 24 home BP readings (7 days and exclusion of the first one) should be routinely obtained, with 12 readings being the minimum acceptable number of home readings (1,35). Readings of the first HBPM day should be discarded, as they are typically higher and more variable than those of the next days' (1,35). For the long-term follow-up of treated hypertensives, HBPM once or twice per week might seem to be appropriate to ensure maintenance of adequate BP control.

## REPORTING OF HOME BLOOD PRESSURE VALUES

Accurate reporting of all systolic/diastolic BP readings and heart rate must be ensured, as it has been shown that HBPM reported by patients frequently differs from the actually measured values (over- or under-reporting of self-measurements) (36). Therefore, home monitors with automated storage of all BP readings in memory or PC download are preferred (1–4). Patients should be asked to record all their HBPM readings in a prepared form according to the recommended schedule.

## DIAGNOSTIC THRESHOLD AND INTERPRETATION

Based on the available evidence derived from meta-analyses of cross-sectional and also long-term observational studies, the current European guidelines recommend a hypertension threshold for average home BP at  $135/85$  mmHg, which is the same as recommended for awake ABPM (1,3). Average levels exceeding this threshold are considered elevated. Average home BP levels ranging between  $130\text{--}135$  mmHg for systolic and  $80\text{--}85$  mmHg for diastolic BP are regarded as borderline, and those  $<130/80$  mmHg as normal (1,3). The 2017 US guidelines recommend a threshold at  $130/80$  mmHg for confirmation of hypertension or uncontrolled treated hypertension (4), which in fact is in line with normal home BP according to the European recommendations (3).

## SUMMARY

European and US guidelines strongly recommend HBPM for out-of-office BP evaluation in almost all patients with elevated BP, with a similar role as ABPM. Accumulating evidence on the diagnostic accuracy and prognostic value of HBPM suggests its primary role in hypertension diagnosis and management, which is further augmented by its wide availability, low cost and good acceptance by patients.

## REFERENCES

1. Parati G, Stergiou GS, Asmar R et al. European Society of Hypertension guidelines for blood pressure monitoring at home: A summary report of the Second International Consensus Conference on Home Blood Pressure Monitoring. *J Hypertens* 2008; 26: 1505–1526.
2. Pickering TG, Miller NH, Oggedegbe G et al. Call to action on use and reimbursement for home blood pressure monitoring: A joint scientific statement from the American Heart



- Association, American Society of Hypertension, and Preventive Cardiovascular Nurses Association. *Hypertension* 2008; 52: 10–29.
3. Mancia G, Fagard R, Narkiewicz K et al. ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1281–1357.
  4. Whelton PK, Carey RM, Aronow WS et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2017; 71(6): 1269–1324.
  5. Stergiou GS, Kollias A, Zeniodi M et al. Home blood pressure monitoring: Primary role in hypertension management. *Curr Hypertens Rep* 2014; 16: 462.
  6. Stergiou GS, Kollias A. Home monitoring of blood pressure. In: Bakris G, Sorrentino M (eds). *Hypertension: A Companion to Braunwald's Heart Disease*, 3rd edn. Philadelphia, US: Elsevier. 2018;89–95.
  7. O'Brien E, Parati G, Stergiou G et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens* 2013; 31: 1731–1768.
  8. Stergiou GS, Bliziotis IA. Home blood pressure monitoring in the diagnosis and treatment of hypertension: A systematic review. *Am J Hypertens* 2011; 24: 123–134.
  9. Stergiou GS, Baibas NM, Gantzarou AP et al. Reproducibility of home, ambulatory, and clinic blood pressure: Implications for the design of trials for the assessment of antihypertensive drug efficacy. *Am J Hypertens* 2002; 15: 101–104.
  10. Stergiou GS, Ntineri A, Kollias A et al. Changing relationship among clinic, home, and ambulatory blood pressure with increasing age. *J Am Soc Hypertens* 2015; 9: 544–552.
  11. Bliziotis IA, Destounis A, Stergiou GS. Home versus ambulatory and office blood pressure in predicting target organ damage in hypertension: A systematic review and meta-analysis. *J Hypertens* 2012; 30: 1289–1299.
  12. Fuchs SC, Mello RG, Fuchs FC. Home blood pressure monitoring is better predictor of cardiovascular disease and target organ damage than office blood pressure: A systematic review and meta-analysis. *Curr Cardiol Rep* 2013; 15: 413.
  13. Stergiou GS, Siontis KC, Ioannidis JP. Home blood pressure as a cardiovascular outcome predictor: It's time to take this method seriously. *Hypertension* 2010; 55: 1301–1303.
  14. Ward AM, Takahashi O, Stevens R et al. Home measurement of blood pressure and cardiovascular disease: Systematic review and meta-analysis of prospective studies. *J Hypertens* 2012; 30: 449–456.
  15. Stergiou GS, Asayama K, Thijs L et al. Prognosis of white-coat and masked hypertension: International database of home blood pressure in relation to cardiovascular outcome. *Hypertension* 2014; 63: 675–682.
  16. Juhanoja EP, Niiranen TJ, Johansson JK et al. Outcome-driven thresholds for increased home blood pressure variability. *Hypertension* 2017; 69: 599–607.
  17. Cappuccio FP, Kerry SM, Forbes L et al. Blood pressure control by home monitoring: Meta-analysis of randomised trials. *BMJ* 2004; 329: 145.
  18. Agarwal R, Bills JE, Hecht TJ et al. Role of home blood pressure monitoring in overcoming therapeutic inertia and improving hypertension control: A systematic review and meta-analysis. *Hypertension* 2011; 57: 29–138.
  19. Niiranen TJ, Kantola IM, Vesalainen R et al. A comparison of home measurement and ambulatory monitoring of blood pressure in the adjustment of antihypertensive treatment. *Am J Hypertens* 2006; 19: 468–474.
  20. Stergiou GS, Karpettas N, Destounis A et al. Home blood pressure monitoring alone vs. combined clinic and ambulatory measurements in following treatment-induced changes in blood pressure and organ damage. *Am J Hypertens* 2014; 27: 184–192.
  21. Omboni S, Gazzola T, Carabelli G et al. Clinical usefulness and cost effectiveness of home blood pressure telemonitoring: Meta-analysis of randomized controlled studies. *J Hypertens* 2013; 31: 455–467.
  22. Margolis KL, Asche SE, Bergdall AR et al. Effect of home blood pressure telemonitoring and pharmacist management on blood pressure control: A cluster randomized clinical trial. *JAMA* 2013; 310: 46–56.
  23. Kollias A, Stergiou GS. Automated measurement of office, home and ambulatory blood pressure in atrial fibrillation. *Clin Exp Pharmacol Physiol* 2014; 41: 9–15.
  24. Stergiou GS, Kollias A, Destounis A et al. Automated blood pressure measurement in atrial fibrillation: A systematic review and meta-analysis. *J Hypertens* 2012; 30: 2074–2082.
  25. Verberk WJ, Omboni S, Kollias A et al. Screening for atrial fibrillation with automated blood pressure measurement: Research evidence and practice recommendations. *Int J Cardiol* 2016; 203: 465–473.
  26. National Institute for Health and Care Excellence 2013. WatchBP Home A for opportunistically detecting atrial fibrillation during diagnosis and monitoring of hypertension. Medical technologies guidance [MTG13]. <https://www.nice.org.uk/guidance/mtg13>
  27. Kollias A, Ntineri A, Stergiou GS. Association of night-time home blood pressure with night-time ambulatory blood pressure and target-organ damage: A systematic review and meta-analysis. *J Hypertens* 2017; 35: 442–452.
  28. Mancia G, Facchetti R, Bombelli M et al. Long-term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure. *Hypertension* 2006; 47: 846–853.
  29. Satoh M, Asayama K, Kikuya M et al. Long-term stroke risk due to partial white-coat or masked hypertension based on home and ambulatory blood pressure measurements: The Ohasama Study. *Hypertension* 2016; 67: 48–55.
  30. Association for the Advancement of Medical Instrumentation 1987. American National Standard. Electronic or automated sphygmomanometers ANSI/AAMI SP10-1987. 3330 Washington Boulevard, Suite 400, Arlington, VA 22201-4598, USA: AAMI.
  31. O'Brien E, Petrie J, Littler W et al. The British Hypertension Society Protocol for the evaluation of automated and semi-automated blood pressure measuring devices with special reference to ambulatory systems. *J Hypertens* 1990; 8: 607–619.
  32. O'Brien E, Pickering T, Asmar R et al. Working Group on Blood Pressure Monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices in adults. *Blood Press Monit* 2002; 7: 3–17.
  33. O'Brien E, Atkins N, Stergiou G et al. European Society of Hypertension International Protocol revision 2010 for the Validation of Blood Pressure Measuring Devices in Adults. *Blood Press Monit* 2010; 15: 23–38.
  34. Juhanoja EP, Puukka PJ, Johansson JK et al. The impact of the day of the week on home blood pressure: The Finn-Home study. *Blood Press Monit* 2016; 21: 63–68.
  35. Stergiou GS, Nasothimiou EG, Kalogeropoulos PG et al. The optimal home blood pressure monitoring schedule based on the Didima outcome study. *J Hum Hypertens* 2010; 24: 158–164.
  36. Myers MG, Stergiou GS. Reporting bias: Achilles' heel of home blood pressure monitoring. *J Am Soc Hypertens* 2014; 8: 350–357.



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# DAY-NIGHT RELATED EVENTS: NIGHTTIME BLOOD PRESSURE FALL AND MORNING BLOOD PRESSURE RISE

# 26

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## INTRODUCTION

Ambulatory blood pressure monitoring (ABPM) is accepted as an indispensable technique to good clinical practice (1,2). When compared to office blood pressure (BP) measurement, ABPM has many advantages, providing a direct record of BP throughout the entire day in patients engaged in their usual activities (3). First and foremost, frequent readings during wakefulness and sleep enable clinicians to obtain a more precise estimation of a patient's BP in the outpatient setting, including the evaluation of BP variability and circadian BP profile (1-7).

In this context, ABPM can identify patients with abnormal patterns of nocturnal BP and can also provide informative indices of BP fluctuations from night to day that are associated with outcome.

Historically, average 24-hour, daytime (awake), and nighttime (asleep) BP values have been the principal components of the ambulatory BP profile to be investigated as prognostic markers (8,9). However, the ability to handle large volumes of data with computer-assisted analysis has led to studies that evaluated different aspects of ambulatory readings during the day and the night windows (4,5). Thus, new indices emerged, including 'nocturnal BP dipping' and 'morning surge in BP' (3,8,9). We specifically address the available evidence provided in this regard by cross-sectional and longitudinal studies to support the notion that not only 24-hour average BP values, but also specific day-night BP components, may have clinical relevance.

To this purpose, we searched for clinical studies using research methodology filters (10). The following research terms were used: 'hypertension', 'BP monitoring, ambulatory', 'circadian profile', 'day-night BP', 'morning BP surge', and 'prognosis'. We also checked the reference list of identified articles and previous systematic reviews to find other relevant studies.

## DAY-NIGHT BLOOD PRESSURE CHANGES

Intra-arterial studies with beat-to-beat recording in ambulant subjects showed that, in the normal individual, there

is a decline in BP in the nighttime window from daytime levels of BP. Usually, a normal circadian pattern shows BP values tending to peak during the daytime hours and then falling to a nadir at night (11,12).

In such a context, ABPM appears to be a valid tool to investigate the diurnal BP changes associated with the sleep-wake cycle, because it has been demonstrated that intra-arterial 24-hour BP profile is similar in the absence and in the presence of concomitant noninvasive BP monitoring (13).

The 'dipper/non-dipper' classification was first introduced in 1988 when a retrospective study suggested that non-dipping patients had an increased risk of stroke over patients with a dipping pattern (14). Usually, 'non-dippers' are defined by a reduction in BP by less than a given percentage from day to night, and the subjects outside of this definition are classified as 'dippers'. The threshold values for classification ranged from 10% to 10/5 mmHg, up to 0% (i.e. no reduction in BP from day to night or a higher BP during night than during day) (15). To date, it has become customary to regard as non-dippers and dippers individuals with a fall of mean nighttime BP <10% and  $\geq 10\%$  than the average daytime values, respectively (7). Dippers may also be defined by a night/day BP ratio  $\leq 0.9$  (7).

Cross-sectional reports from independent centers showed that prevalence of renal and cardiac target organ involvement, including left ventricular hypertrophy (16) and microalbuminuria (17), was higher among subjects with blunted or abolished fall in BP from day to night than individuals with normal day-night BP difference.

A non-dipping nocturnal pattern is also associated with angiographic coronary artery stenosis in men (18), cerebrovascular disease (14,19) and lower cognitive performance (20).

Moreover, several studies demonstrated the prognostic value of nighttime BP and day-night BP changes (particularly in individuals whose nocturnal BP remains elevated) (21) and it is now generally accepted that a diminished nocturnal BP fall is associated with a poor prognosis. Furthermore, day-night BP changes significantly refined cardiovascular risk stratification above office BP and other traditional risk markers (22,23).

Yamamoto et al. (24) demonstrated that the degree of ambulatory BP reduction from day to night at the baseline assessment was significantly ( $p < 0.01$ ) smaller in the group with subsequent cerebrovascular events than in the group with no future events.

In older patients with isolated systolic hypertension, the Systolic Hypertension in Europe (Syst-Eur) study found that cardiovascular risk increased with a higher night/day ratio of systolic BP (i.e. in patients more likely to be non-dippers) independent of the average 24-hour BP (25).

Similarly, Ohkubo et al. (26) showed an increased cardiovascular mortality in 'non-dippers' (relative risk [RR]: 2.56,  $p = 0.02$ ) and 'reverse-dippers' (RR: 3.69,  $p = 0.004$ ) in comparison with 'dippers'.

Furthermore, in some patients BP is actually higher during night than during day. This phenomenon is usually referred as 'reverse dipping' and is associated with an adverse cardiovascular outcome (27).

In this context, a recent analysis of the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) Study confirmed on a large sample of 3792 subjects the detrimental effect of 'reverse dipping' in hypertension. Briefly, the rates of cardiovascular events were 0.57 (95% CI: 0.36–0.88), 0.76 (95% CI: 0.63–0.92), 1.65 (95% CI: 1.37–1.98), and 3.06 (95% CI: 2.10–4.46)  $\times$  100 patient-years in the categories of extreme dippers, dippers, non-dippers, and reverse dippers, respectively (log-rank  $\chi^2 = 74.8$ ;  $p < 0.0001$ ). After adjustment for multiple comparisons, failure rate was higher in non-dippers (log-rank  $\chi^2 = 33.1$ ;  $p < 0.0001$ ) and reverse dippers (log-rank  $\chi^2 = 39.6$ ;  $p < 0.0001$ ) as compared with dippers, whereas extreme dippers and dippers did not differ significantly (log-rank  $\chi^2 = 3.8$ ;  $p < 0.052$ ).

Finalizing our discussion of the prognostic implications of a blunted or abolished fall in BP from day to night, at least three aspects need to be clearly detailed. First, the prognostic value of the diurnal BP changes is comparable when using different clock-dependent or independent definitions of day and night (23). A recent analysis from our group (23) documented that total cardiovascular events and all-cause mortality were similarly higher in non-dippers (night/day ratio of systolic BP  $>10\%$  or  $>0\%$ ) than in dippers regardless of the definition of day and night. Specifically, in a receiver-operated characteristic (ROC) curve analysis of the night/day ratio of systolic BP on the occurrence of events, the area under the ROC curve did not differ among the different definitions of day and night (large fixed-clock intervals, narrow fixed-clock intervals, diary) for both total cardiovascular events ( $p = 0.20$ ) and all-cause mortality ( $p = 0.78$ ) (23).

Second, nighttime BP may lose its prognostic significance in hypertensive subjects with significant sleep disturbances during overnight monitoring that may occur for the compressive, tactile and sonorous stimuli produced by repeated cuff inflations (28).

Recent findings supported this hypothesis, suggesting that the prognostic impact of day-night BP changes should be investigated, including the perceived quantity of sleep as effect modifier in outcome analyses (28). Specifically, in a recent analysis of the PIUMA database we followed 2934 initially untreated hypertensive subjects and we assessed the perceived quantity of sleep during overnight BP monitoring (28). Overall, 58.7%, 27.7%, 9.7% and 4.0%

of subjects reported a sleep duration perceived as usual (group A),  $<2$  hours less than usual (group B), 2–4 hours less than usual (group C), and  $>4$  hours less than usual (group D). Daytime BP did not differ across the groups (all  $p > 0.05$ ). Nighttime BP increased from group A to D (124/75, 126/76, 128/77, and 129/79 mmHg, respectively; all  $p$  for trend  $<0.01$ ). Over a median follow-up period of 7 years there were 356 major cardiovascular events and 176 all-cause deaths. Incidence of total cardiovascular events and deaths was higher in the subjects with a night/day ratio in systolic BP  $>10\%$  compared with those with a greater day-night BP drop in the group with perceived sleep duration as usual or  $<2$  hours less than usual (both  $p < 0.01$ ), not in the group with duration of sleep  $\geq 2$  hours less than usual (all  $p$  not significant; Figure 26.1). Notably, in a Cox model, the independent prognostic value of nighttime BP for total cardiovascular endpoints and all-cause mortality disappeared in the subjects with perceived sleep deprivation  $\geq 2$  hours.

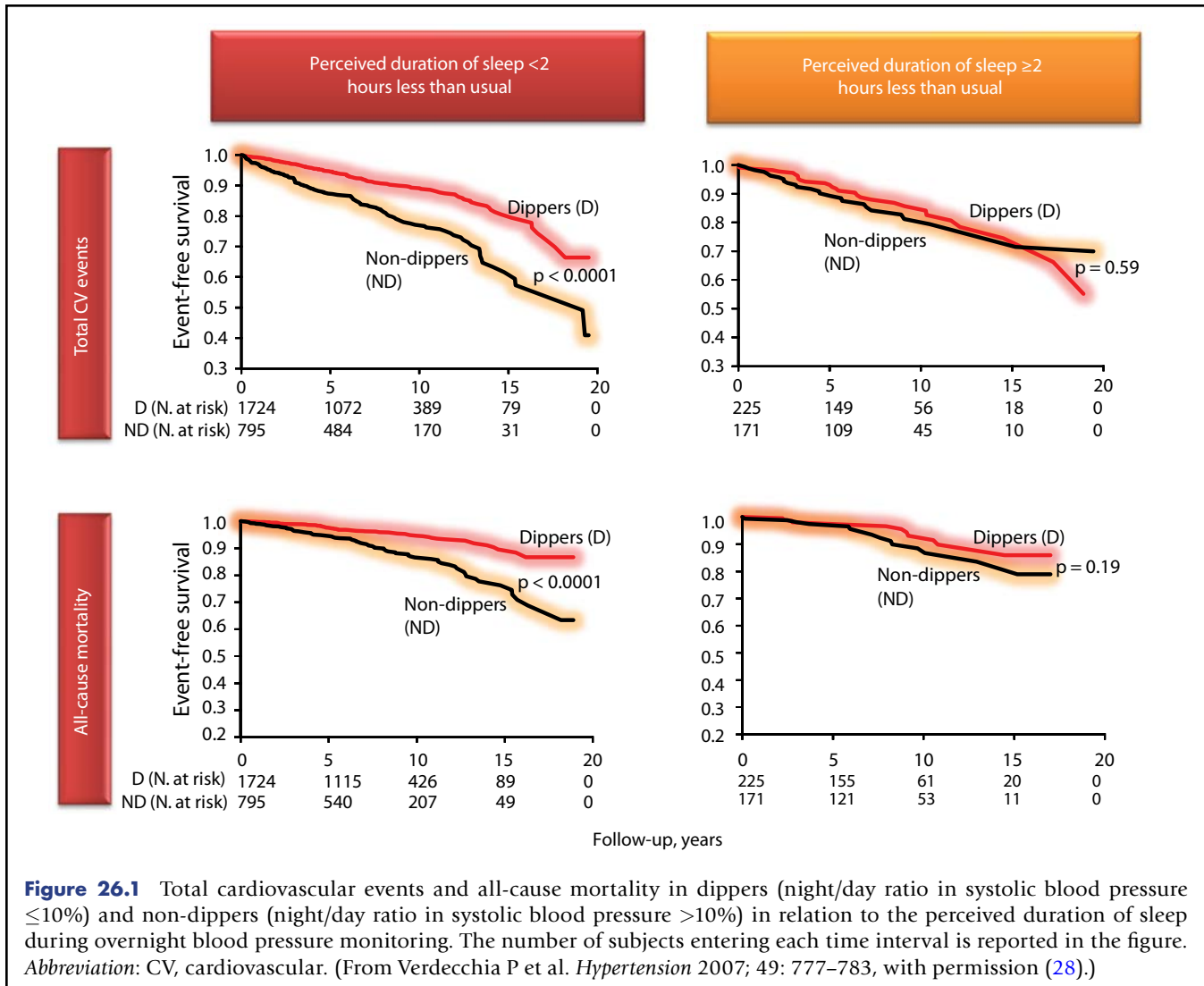
Finally, additional support to the prognostic independent importance of night BP measurements comes from the evidence that absolute nighttime BP values are prognostically superior to the daytime ones (29–32) and that abnormal nighttime BP fluctuations may contribute to a worse prognosis in hypertensive patients (33).

In this context, a large multinational cooperative database including 7112 untreated hypertensive patients enrolled in six prospective studies (33) demonstrated that nighttime BP variability (as estimated by standard deviation [SD]) was an independent predictor of all-cause mortality, cardiovascular mortality, and cardiovascular events. In contrast, daytime BP variability was not an independent predictor of outcomes in any multivariable model. Specifically, in fully adjusted models, a nighttime systolic BP SD  $\geq 12.2$  mmHg was associated with a 41% greater risk of cardiovascular events, a 55% greater risk of cardiovascular death, and a 59% increased risk of all-cause mortality compared with an SD  $<12.2$  mmHg. The corresponding values for a diastolic BP SD of  $\geq 7.9$  mmHg were 48%, 132% and 77%, respectively. The addition of nighttime BP variability to fully adjusted models had a significant impact on risk reclassification and integrated discrimination for all outcomes (relative integrated discrimination improvement for systolic BP variability: 9% cardiovascular events, 14.5% all-cause death, 8.5% cardiovascular death; for diastolic BP variability: 10% cardiovascular events, 19.1% all-cause death, 23% cardiovascular death, all  $p < 0.01$ ).

## EARLY MORNING BLOOD PRESSURE SURGE

Through ABPM, we know that BP usually follows a distinct circadian rhythm, characterized by a nocturnal decline during sleep followed by an increase coinciding with the time of awakening (26,27). In the last few years, there has been great interest in the early morning period by preventive medicine, since it became evident that the onset of sudden death, myocardial infarction and stroke peaks in the first 4–6 hours post-awakening (26,27).

Since dynamic diurnal variations in pressor stress from a nadir in the night to a peak in the morning (the morning



surge in BP) and some cardiovascular events all follow the same temporal pattern, it has been hypothesized that a pathophysiologic relationship exists between hemodynamic aberrations such as the early morning BP surge and vascular damage (34–37).

Some investigations have been conducted to explore the possible mechanisms of the morning surge in BP and its potential relationship to cardiovascular events (34–37). Increased sympathetic nervous system activity and activation of the renin–angiotensin–aldosterone system (RAAS) may contribute to increase vascular resistance and the morning BP surge. Whether these mechanisms of morning BP elevation independently convey vascular harm is not clear, but of theoretical concern as it is known that alpha-adrenergic stimulation and RAAS activation can increase vascular tone, coronary vasospasm and pro-thrombotic tendencies in the early morning period (34–37). Moreover, risk factors for a profile of excessive early morning hypertension include older age, excessive alcohol and/or smoking, longer sleep times, later awakening times and cold weather climates (38,39).

To date, the following two different estimates of the morning surge in BP proved prognostic significance

(40,41): (i) the sleep-through morning BP surge computed as the difference between the average BP during the 2 hours following awakening and the lowest nighttime BP (i.e. the average of the lowest BP and the two readings immediately preceding and after the lowest value), and (ii) the pre-awakening morning BP surge as the difference between the average BP during the 2 hours after awakening and the average BP during the 2 hours before awakening (Figure 26.2).

Some studies performed in the past decade have found significant relations among the early morning BP surge and vascular disease (42), cardiac hypertrophy (43) and white matter lesions of the brain (40).

Of note, in a population of 519 older hypertensive subjects from Japan who contributed 44 stroke events, during an average follow-up of 41 months, a higher morning BP rise (sleep-through morning surge  $\geq 55$  mmHg) was associated with stroke risk independently of ambulatory BP, nocturnal BP falls and silent cerebral infarct ( $p = 0.008$ ) (40).

More recently, an analysis by the International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome (IDACO) demonstrated that the morning surge



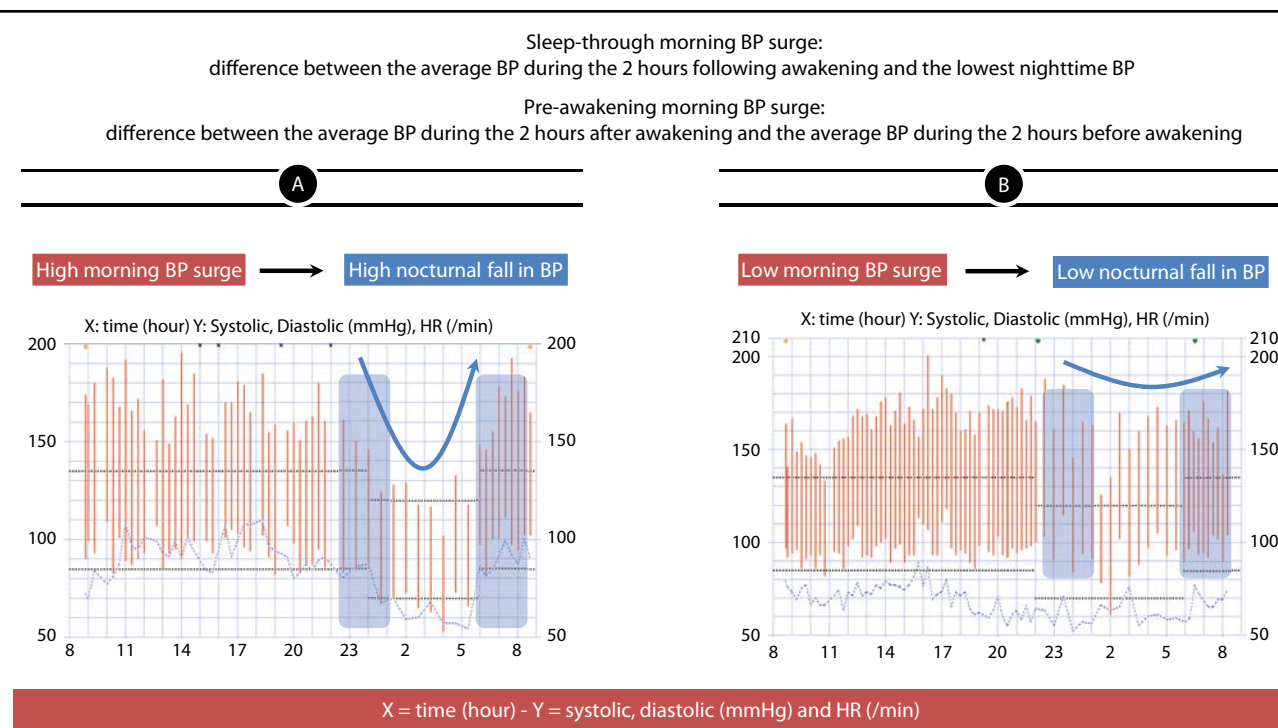


**Figure 26.2** Estimates of the morning blood pressure surge, which proved prognostic significance in some reports. The figure also suggests that day-night reduction in systolic blood pressure may be directly associated with the sleep through or the pre-awakening systolic blood pressure surge (see text for details). *Abbreviation:* BP, blood pressure.

above the 90th percentile (sleep-through morning surge  $\geq 37$  mmHg) significantly and independently predicted cardiovascular outcome and might contribute to risk stratification by ambulatory BP monitoring (41).

In contrast, a recent analysis of the PIUMA study (22) showed that a greater morning BP surge, either expressed as sleep-through or pre-awakening surge, did not predict a greater cardiovascular risk in a large sample of 3012 subjects with hypertension. Unexpectedly, in a multivariable Cox model (after adjustment for several predictive covariates, including age, sex, diabetes mellitus, cigarette smoking, total cholesterol, LV hypertrophy, estimated glomerular filtration rate and average 24-hour systolic BP), a blunted sleep through ( $\leq 19.5$  mmHg) and pre-awakening ( $\leq 9.5$  mmHg) BP surge was associated with an excess risk of events (HR: 1.66, 95% CI: 1.14–2.42, and HR: 1.71, 95% CI: 1.12–2.71, respectively).

These findings were explained by the evidence that the day-night reduction in systolic BP showed a direct association with the sleep through ( $r = 0.564$ ;  $p < 0.0001$ ) and the pre-awakening ( $r = 0.554$ ;  $p < 0.0001$ ) systolic BP surge: the greater the day-night dip, the greater the morning BP surge, and vice versa (22) (Figure 26.2).

Finally, the magnitude of the morning BP rise has recently been found to have no relationship with the risk of cardiovascular events in the population of the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study during a follow-up of 16 years (44).

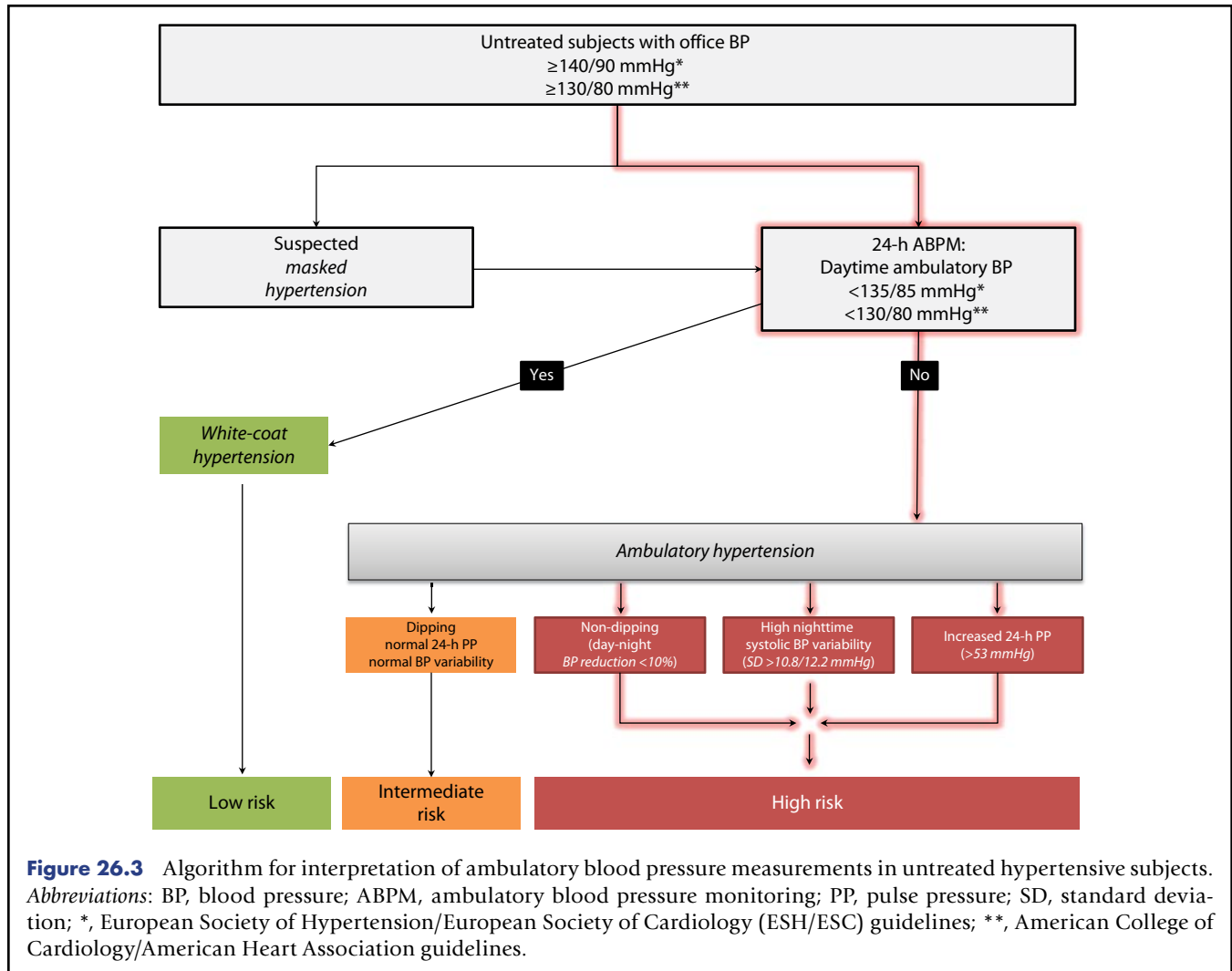
A current working hypothesis is that, because of ethnic differences, the morning BP rise phenomenon may be more pronounced and clinically significant in Asian than in Caucasian individuals (7).

## DAY-NIGHT BLOOD PRESSURE CHANGES IN CLINICAL PRACTICE

The clinical use of ABPM in individual subjects to optimize their management is soundly based. The National Institute for Health and Care Excellence (NICE) was the first to state unequivocally that ABPM should be offered to all people with elevated office BP (45). The U.S. Preventive Services Task Force (USPSTF), an independent panel of experts in prevention and evidence-based medicine, recently suggested offering ABPM to all subjects with elevated office BP at screening and offering antihypertensive treatment solely to subjects with elevated ambulatory BP, not to those with white-coat hypertension (46,47). These conclusions are substantially shared by a position paper of the European Society of Hypertension on ABPM (3). The paper states that, because of its high prevalence and clinical importance, it is extremely important to make an accurate diagnosis of isolated clinical hypertension. This goal 'can best be achieved by performing 24-hour ambulatory BP monitoring and/or home BP monitoring in all patients with uncomplicated, stage 1 and 2 essential hypertension before prescribing antihypertensive drug therapy' (3).

Average 24-hour, daytime (awake) and nighttime (asleep) BP are the principal components of the ambulatory BP profile which proved prognostic significance. Nevertheless, other summary measures exist for describing different aspects of ambulatory readings.

In our opinion, interpretation of ABPM in individual patients to optimize their management must be kept



simple (8,9,48), and clinicians should concentrate on ambulatory components, which proved to substantially refine risk profiling over and beyond the BP level (6,49).

Evidence suggests that only the addition of ambulatory pulse pressure, dipping status and nighttime BP variability to models of long-term outcomes improves risk stratification after accounting for the impact of average ambulatory BP levels (6,8,9,48).

Of note, a recent systematic overview and meta-analysis of prospective studies in adults by Taylor and co-workers (50) evaluated the prognostic significance of some measures of BP variability and day-night BP changes in addition to mean BP. They demonstrated that night dipping based on percentage change was the most researched measure and the only measure for which data was meaningfully pooled to stratify the risk of cardiovascular events over and beyond average ambulatory BP (50).

Such findings reinforce the notion that the correct interpretation and use in clinical practice of ABPM needs a standardization of methods. To this purpose, we developed some algorithms for the clinical use of ambulatory BP monitoring (4,6,8,9,51–57) (Figure 26.3). In such a context, among subjects with elevated daytime BP, a non-dipping status and/or high nighttime systolic BP variability identify high-risk individuals, regardless of office BP

values. In these subjects, drug treatment is highly recommended (6) (Figure 26.3).

## REFERENCES

1. Parati G, Stergiou G, O'Brien E et al. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. *J Hypertens* 2014; 32: 1359–1366.
2. Stergiou GS, Parati G, Vlachopoulos C et al. Methodology and technology for peripheral and central blood pressure and blood pressure variability measurement: Current status and future directions—Position statement of the European Society of Hypertension Working Group on blood pressure monitoring and cardiovascular variability. *J Hypertens* 2016; 34: 1665–1677.
3. O'Brien E, Parati G, Stergiou G et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens* 2013; 31: 1731–1768.
4. Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; 34: 2159–2219.
5. James PA, Oparil S, Carter BL et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the eighth Joint National Committee (JNC 8). *JAMA* 2013; 311(5): 507–520.
6. Angeli F, Reboldi G, Poltronieri C et al. Clinical utility of ambulatory blood pressure monitoring in the management of hypertension. *Expert Rev Cardiovasc Ther* 2014; 12: 623–634.

7. Mancia G, Verdecchia P. Clinical value of ambulatory blood pressure: Evidence and limits. *Circ Res* 2015; 116: 1034–1045.
8. Angeli F, Reboldi G, Verdecchia P. Interpretation of ambulatory blood pressure profile: A prognostic approach for clinical practice. *J Hypertens* 2015; 33: 454–457.
9. Reboldi G, Angeli F, Verdecchia P. Interpretation of ambulatory blood pressure profile for risk stratification: Keep it simple. *Hypertension* 2014; 63: 913–914.
10. Haynes RB, Wilczynski N, McKibbin KA et al. Developing optimal search strategies for detecting clinically sound studies in MEDLINE. *J Am Med Inform Assoc* 1994; 1: 447–458.
11. Littler WA, West MJ, Honour AJ, Sleight P. The variability of arterial pressure. *Am Heart J* 1978; 95: 180–186.
12. Mancia G, Ferrari A, Gregorini L et al. Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. *Circ Res* 1983; 53: 96–104.
13. Parati G, Pomidossi G, Casadei R et al. Ambulatory blood pressure monitoring does not interfere with the haemodynamic effects of sleep. *J Hypertens Suppl* 1985; 3: S107–S109.
14. O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. *Lancet* 1988; 2: 397.
15. Pickering TG. How should the diurnal changes of blood pressure be expressed? *Am J Hypertens* 1995; 8: 681–392.
16. Verdecchia P, Schillaci G, Guerrieri M et al. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. *Circulation* 1990; 81: 528–536.
17. Bianchi S, Bigazzi R, Baldari G et al. Diurnal variations of blood pressure and microalbuminuria in essential hypertension. *Am J Hypertens* 1994; 7: 23–29.
18. Mousa T, el-Sayed MA, Motawea AK et al. Association of blunted nighttime blood pressure dipping with coronary artery stenosis in men. *Am J Hypertens* 2004; 17: 977–980.
19. Kario K, Matsuo T, Kobayashi H et al. Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients. Advanced silent cerebrovascular damage in extreme dippers. *Hypertension* 1996; 27: 130–135.
20. Bellelli G, Frisoni GB, Lucchi E et al. Blunted reduction in nighttime blood pressure is associated with cognitive deterioration in subjects with long-standing hypertension. *Blood Press Monit* 2004; 9: 71–76.
21. Fagard RH, Staessen JA, Thijs L. Prediction of cardiac structure and function by repeated clinic and ambulatory blood pressure. *Hypertension* 1997; 29: 22–29.
22. Verdecchia P, Angeli F, Mazzotta G et al. Day-night dip and early-morning surge in blood pressure in hypertension: Prognostic implications. *Hypertension* 2012; 60: 34–42.
23. Verdecchia P, Angeli F, Borgioni C et al. Prognostic value of circadian blood pressure changes in relation to differing measures of day and night. *J Am Soc Hypertens* 2008; 2: 88–96.
24. Yamamoto Y, Akiguchi I, Oiwa K et al. Adverse effect of nighttime blood pressure on the outcome of lacunar infarct patients. *Stroke* 1998; 29: 570–576.
25. Staessen JA, Thijs L, Fagard R et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA* 1999; 282: 539–546.
26. Ohkubo T, Imai Y, Tsuji I et al. Relation between nocturnal decline in blood pressure and mortality. The Ohasama Study. *Am J Hypertens* 1997; 10: 1201–1207.
27. Kario K, Shimada K. Risers and extreme-dippers of nocturnal blood pressure in hypertension: Antihypertensive strategy for nocturnal blood pressure. *Clin Exp Hypertens* 2004; 26: 177–189.
28. Verdecchia P, Angeli F, Borgioni C et al. Ambulatory blood pressure and cardiovascular outcome in relation to perceived sleep deprivation. *Hypertension* 2007; 49: 777–783.
29. Dolan E, Stanton A, Thijs L et al. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: The Dublin outcome study. *Hypertension* 2005; 46: 156–161.
30. Fagard RH, Celis H, Thijs L et al. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension* 2008; 51: 55–61.
31. Fan HQ, Li Y, Thijs L et al. Prognostic value of isolated nocturnal hypertension on ambulatory measurement in 8711 individuals from 10 populations. *J Hypertens* 2010; 28: 2036–2045.
32. Sega R, Facchetti R, Bombelli M et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: Follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation* 2005; 111: 1777–1783.
33. Palatini P, Reboldi G, Beilin LJ et al. Added predictive value of night-time blood pressure variability for cardiovascular events and mortality: The Ambulatory Blood Pressure-International Study. *Hypertension* 2014; 64: 487–493.
34. White WB. Clinical assessment of early morning blood pressure in patients with hypertension. *Prev Cardiol* 2007; 10: 210–214.
35. Hoshida S, Kario K. Early morning hypertension: A narrative review. *Blood Press Monit* 2013; 18: 291–296.
36. Hoshida S, Kario K. [Early morning hypertension/morning blood pressure surge]. *Nihon Rinsho* 2014; 72: 1395–1399.
37. Kario K, White WB. Early morning hypertension: What does it contribute to overall cardiovascular risk assessment? *J Am Soc Hypertens* 2008; 2: 397–402.
38. Modesti PA, Morabito M, Bertolozzi I et al. Weather-related changes in 24-hour blood pressure profile: Effects of age and implications for hypertension management. *Hypertension* 2006; 47: 155–161.
39. Murakami S, Otsuka K, Kubo Y et al. Repeated ambulatory monitoring reveals a Monday morning surge in blood pressure in a community-dwelling population. *Am J Hypertens* 2004; 17: 1179–1183.
40. Kario K, Pickering TG, Umeda Y et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: A prospective study. *Circulation* 2003; 107: 1401–1406.
41. Li Y, Thijs L, Hansen TW et al. Prognostic value of the morning blood pressure surge in 5645 subjects from 8 populations. *Hypertension* 2010; 55: 1040–1048.
42. Marfella R, Siniscalchi M, Nappo F et al. Regression of carotid atherosclerosis by control of morning blood pressure peak in newly diagnosed hypertensive patients. *Am J Hypertens* 2005; 18: 308–318.
43. Gosse P, Ansoborlo P, Lemetayer P, Clementy J. Left ventricular mass is better correlated with arising blood pressure than with office or occasional blood pressure. *Am J Hypertens* 1997; 10: 505–510.
44. Bombelli M, Fodri D, Toso E et al. Relationship among morning blood pressure surge, 24-hour blood pressure variability, and cardiovascular outcomes in a white population. *Hypertension* 2014; 64: 943–950.
45. National Clinical Guideline Centre (UK). *Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18 and 34 [Internet]*. [abstract] London: Royal College of Physicians (UK); 2011.
46. Piper MA, Evans CV, Burda BU et al. Diagnostic and predictive accuracy of blood pressure screening methods with consideration of rescreening intervals: A systematic review for the U.S. Preventive services task force. *Ann Intern Med* 2015; 162: 192–204.
47. Verdecchia P, Angeli F, Bartolini C, Reboldi G. Twenty-four hour ambulatory blood pressure monitoring to all? Comments to the US Preventive Services Task Force document. *J Am Soc Hypertens* 2015; 9: 911–915.
48. Angeli F, Verdecchia P, Poltronieri C et al. Ambulatory blood pressure monitoring in the elderly: Features and perspectives. *Nutr Metab Cardiovasc Dis* 2014; 24: 1052–1056.
49. Verdecchia P, Garofoli M, Angeli F, Reboldi G. Response to morning surge, dipping, and sleep-time blood pressure as prognostic markers of cardiovascular risk. *Hypertension* 2013; 61: e4.
50. Taylor KS, Heneghan CJ, Stevens RJ et al. Heterogeneity of prognostic studies of 24-hour blood pressure variability: Systematic review and meta-analysis. *PLOS ONE* 2015; 10: e0126375.
51. Angeli F, Reboldi G, Repaci S et al. [Ambulatory blood pressure monitoring in clinical practice]. *G Ital Cardiol (Rome)* 2008; 9: 402–407.
52. Verdecchia P, Angeli F. How can we use the results of ambulatory blood pressure monitoring in clinical practice? *Hypertension* 2005; 46: 25–26.
53. Verdecchia P, Angeli F, Cavallini C. Ambulatory blood pressure for cardiovascular risk stratification. *Circulation* 2007; 115: 2091–2093.
54. Verdecchia P, Angeli F, Gattobigio R. Clinical usefulness of ambulatory blood pressure monitoring. *J Am Soc Nephrol* 2004; 15(Suppl. 1): S30–S33.
55. Verdecchia P, Angeli F, Gattobigio R, Porcellati C. Ambulatory blood pressure monitoring and prognosis in the management of essential hypertension. *Expert Rev Cardiovasc Ther* 2003; 1: 79–89.
56. Verdecchia P, Angeli F, Staessen JA. Compared with whom? Addressing the prognostic value of ambulatory blood pressure categories. *Hypertension* 2006; 47: 820–821.
57. Whelton PK, Carey RM, Aronow WS et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017; 71(6): 1269–1324.

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## INTRODUCTION

Blood pressure (BP) values change significantly over the 24-hour period as a result of the interaction between extrinsic environmental and behavioural factors and intrinsic cardiovascular regulatory mechanisms. Although these variations represent a continuous phenomenon, they may be evaluated over different time windows: (1) in the very short term, by focusing on BP changes occurring beat-by-beat when implementing continuous BP recordings (very-short-term blood pressure variability [BPV]); or (2) in the short term on the basis of 24-hour ambulatory BP monitoring (ABPM) which allows evaluating either reading-by-reading BP changes (faster short-term BPV) or slower BP changes associated with circadian rhythms (day-night BP changes, morning surge) or with behavioural factors (e.g. job-related or postprandial, siesta-related BP changes). Although in physiological conditions different types of short-term BP variations may represent a response to environmental stimulations from daily life, they may also reflect alterations in mechanisms responsible for cardiovascular homeostasis or the presence of underlying pathological conditions associated with autonomic dysfunction. Over the last few decades, a series of experimental and clinical studies have indicated that increases in indices of overall short-term BPV and alterations in patterns of circadian BPV (i.e. impaired day-to-night BP profiles) are associated with development, progression and severity of cardiac, vascular, cerebral and renal organ damage and with an increased risk of cardiovascular events and cardiovascular and all-cause mortality (Figure 27.1). This chapter reviews the current available evidence in the field of short-term BPV including its mechanisms, the methodological aspects that should be considered for its assessment, the indices for its estimation, its relevance and significance for cardiovascular prognosis as well as its potential for application in clinical practice.

## MECHANISMS

In physiological conditions, BP fluctuations occurring beat-by-beat and within 24 hours may represent a homeostatic response of neural (1–3), humoral, vascular (4–7)

and rheological mechanisms to extrinsic environmental, behavioural and emotional stimuli. This response might also be modulated by a genetically determined susceptibility not yet completely understood. Of note, normotensive offspring of hypertensive parents exhibit exaggerated sympathetic activation and blood pressure responses upon mental stress (8). However, when increases in short-term BPV are sustained, they may also reflect alterations in regulatory mechanisms in the context of pathological conditions associated with autonomic dysfunction, characterized by enhanced sympathetic drive and impaired baroreflex function or by more complex neurological disorders. A list of the intrinsic cardiovascular mechanisms and extrinsic factors responsible for BP fluctuations occurring in the very short term and in the short term are summarized in Figure 27.1. In particular, alterations in autonomic cardiovascular modulation, behavioural factors of the individual such as daytime levels of activity, and overall changes in the sleep/wakefulness cycle have been shown to exert an important influence on slower short-term BPVs occurring from day to night. For instance, alterations in nighttime BP patterns (i.e. non-dipping or rising pattern of BP) have been shown to be influenced not only by an increased sympathetic activity during nighttime (3,9) but also by salt sensitivity and sodium excretion (10,11), sleep-related breathing disorders, obesity and insulin resistance (12), endothelial dysfunction (13) or specific drug intake (14,15).

## METHODS FOR ASSESSMENT OF SHORT-TERM BLOOD PRESSURE VARIABILITY

BP variations occurring over 24 hours may be evaluated in the very short term using beat-by-beat continuous BP recordings, or in the short term through 24-hour ABPM. The latter approach allows assessing both faster short-term BPV (reading-by-reading BP changes) and slower short-term BPV (i.e. BP changes associated with circadian rhythms or with behavioural factors). An accurate assessment of fast BP fluctuations occurring in the very short term, either in the laboratory setting or under ambulatory conditions, requires implementation of continuous beat-to-beat BP recordings over variable recording periods (i.e.



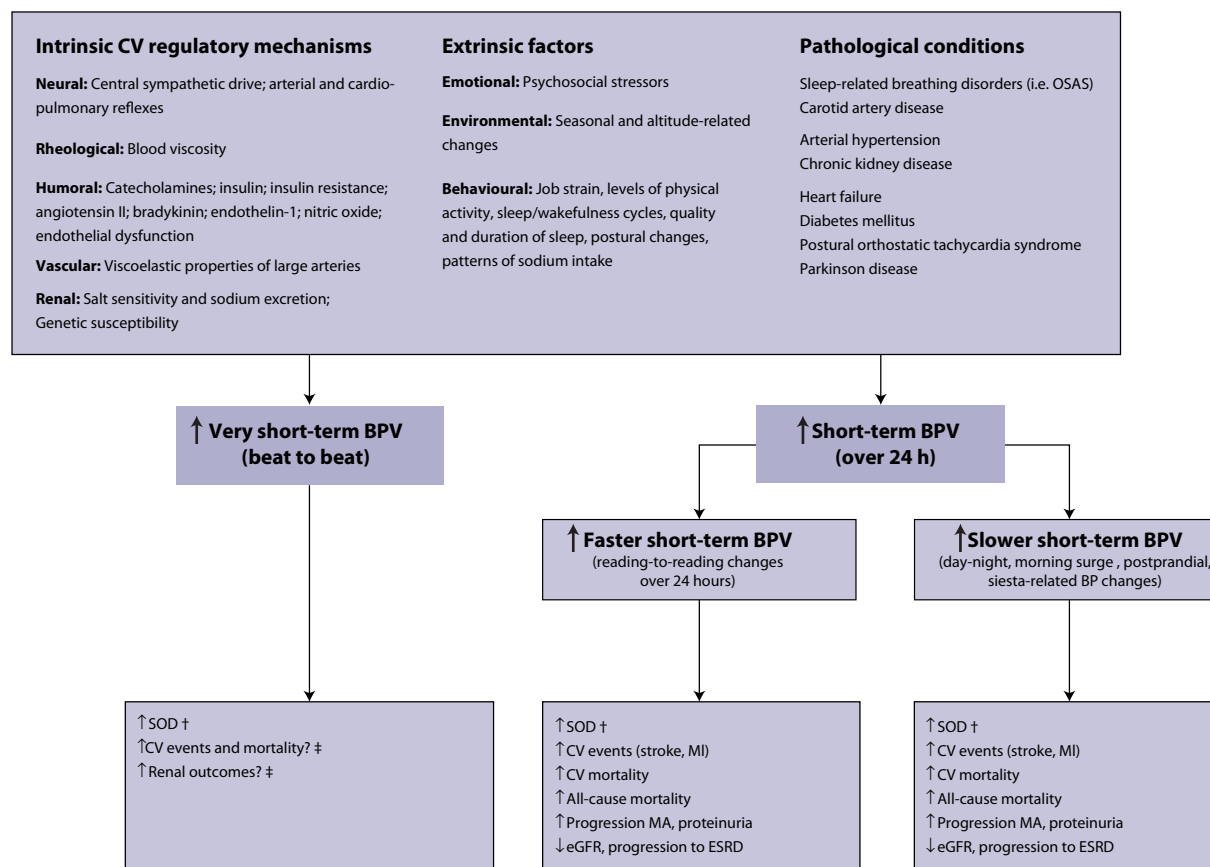


**Figure 27.1** Different types of short-term BPV, their determinants and prognostic relevance. Arrows indicate an increase in cardiovascular complications associated with an increased BPV. †Cardiac, vascular, and renal SOD; ‡BPV on a beat-by-beat basis has not been routinely measured in population studies. *Abbreviations:* AHT, antihypertensive treatment; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IHD, ischaemic heart disease; MA, microalbuminuria; MI, myocardial infarction; SOD, subclinical organ damage.

1 min to 24 h). Indeed, it was through the use of 24-hour intra-arterial BP monitoring in ambulant subjects (the so-called Oxford system) that these BP fluctuations occurring on a beat-by-beat basis and over the 24-hour period were first identified (16). These recordings allowed both the identification of wake-to-sleep BP variations (i.e. nocturnal BP fall during sleep followed by a rapid BP increase in the early morning hours, with an additional BP decrease in the early afternoon during siesta) and documentation of fast changes in BP levels occurring during physical exercise and under the effects of behavioural and emotional stimuli (17). Increasing concerns about the invasive nature and methodological difficulties of intra-arterial BP monitoring led to the development of the vascular unloading technique by Penaz and Wesseling (18) which paved the way to create the first noninvasive prototype for continuous BP measurement using this principle (19). A device based on this method became commercially available as Finapres (TNO, Amsterdam, the Netherlands), with several subsequent devices being built based on the same principle (Finometer [Finapres Medical Systems, Amsterdam, the Netherlands], Nexfin HD [BMEYE B.V., Amsterdam, the Netherlands], and Task Force Monitor [CNSystems, Graz, Austria]). Through the use of finger cuffs equipped with an infrared photoplethysmograph and sophisticated

technology for the calibrated quantification of finger BP, this device allows measuring BP levels on a beat-to-beat basis, providing the possibility to track fast variations in BP values either spontaneously occurring or during stimulated conditions in the laboratory setting (20). A portable version of the Finometer (Portapres; Finapres Medical Systems, Amsterdam, the Netherlands) (21) is currently available, which permits a continuous, nonstationary measurement of BP during 24 hours at the finger level in ambulant subjects and outside of the laboratory setting. Continuous BP recordings performed within 24 hours represent the most accurate approach for the assessment of different indices of very short- and short-term BPV (see below). However, the difficulties in implementing continuous invasive recordings outside the laboratory setting in a daily life situation, the instability of measurements and the cost and technical difficulties in performing noninvasive beat-by-beat recordings have thus far prevented this method from being widely used in clinical practice. While an accurate assessment of fast BP fluctuations occurring in the very short term is only possible through implementation of continuous beat-to-beat BP recordings, evaluation is also possible (although less precisely) through the use of intermittent, noninvasive 24-hour ABPM with intervals between measurements from 15 to 20–30 min (22,23). This allows the straightforward



estimation of short-term BPV for the whole 24-hour period and separately for the daytime and nighttime subperiods (which represents a major advantage of 24-hour ABPM if the important prognostic value of nighttime BP changes is considered). Important aspects to be considered for estimation of short-term BPV from ABPM include measurement intervals and criteria for determining day- and nighttime periods (predefined wide-fixed or narrow-fixed time periods, self-reported diaries, actigraphy), as well as the BPV metrics to be analysed, and whether individuals' behaviours should be standardized in terms of daily activities, time in bed, working and resting hours, physical activity, etc. Regarding determination of the interval between measurements and the minimum number of BP measurements to be obtained over 24 hours, the analysis of a large 24-hour ABPM registry found 48 BP readings (spaced at 15- and 30-min intervals during day and night, respectively) to be the minimum number of BP readings required to compute short-term BPV (i.e. as estimated by calculating average real variability [ARV]) without loss of prognostic information (24). However, such a relatively small number of readings may be responsible for inaccuracies, as shown by a simulation study carried out on 24-hour intra-arterial recordings (25). Given that highly frequent measurements might cause discomfort, thus reducing compliance and acceptance of ABPM, measurements at 15- to 20-minute intervals could be a reasonable compromise for BPV assessment in clinical

practice. Regarding the definition of the daytime (awake) and nighttime (asleep) periods, a study with ABPM in 330 participants showed that there was a high degree of agreement between the definitions of both periods by actigraphy and by self-reporting, with the narrow-fixed-time periods representing an alternative acceptable approach (26). Editing of possible artefactual readings is not recommended at present, but percent of automatically accepted readings should be reported. Appropriate implementation of ABPM according to current recommendations is critical for the proper estimation of BPV indices, either for research purposes or in a clinical setting (24,27–30). Table 27.1 summarizes some important aspects regarding the assessment of very-short- and short-term BPV in clinical practice.

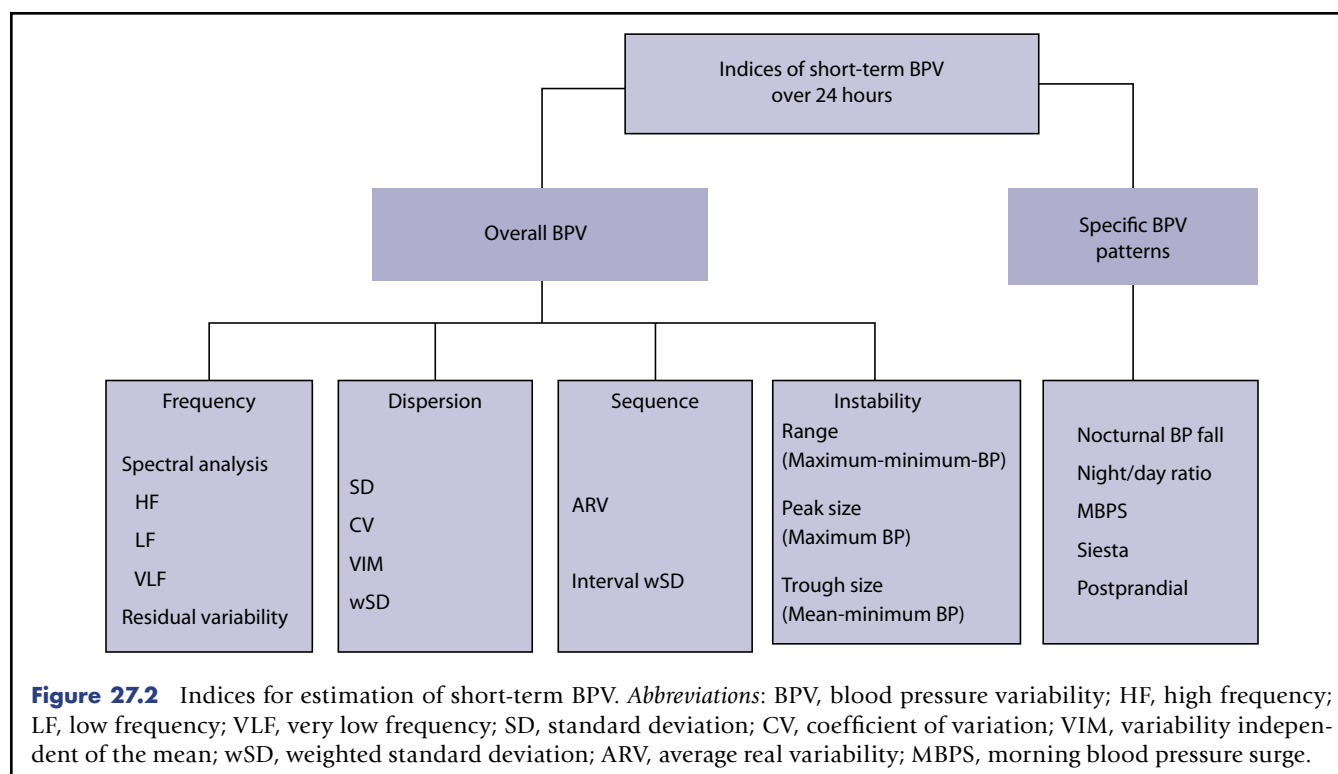
### INDICES FOR ESTIMATION OF BLOOD PRESSURE VARIABILITY

In general, indices for assessment of BPV over 24 hours can be classified into two main groups: (1) *indices of overall variability*, focusing on faster BP variations occurring reading-to-reading over the 24-hour period, which assess either the frequency components of BP spectra in the frequency domain, or in the time domain, the degree of dispersion, the sequence or the instability of BP values over a certain

**Table 27.1** Methods for assessment of very short- and short-term BPV

| Characteristic features      | Very short-term BPV (beat by beat)                                                                                       | Short-term BPV (within 24 h)                                                                                                                                                                                         |
|------------------------------|--------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Method for BP measurement    | Continuous BP recordings in a laboratory setting or under ambulatory conditions                                          | Validated ABPM devices                                                                                                                                                                                               |
| Measurement intervals        | Beat-to-beat                                                                                                             | 15–20-min intervals for day and night, respectively<br>A 15-min interval for the whole 24-h time desirable but not always feasible                                                                                   |
| Number of measurements       | Variable depending on patient's heart rate and recording duration                                                        | Ideally 87–96, at least 72 valid measurements when focusing on BPV                                                                                                                                                   |
| Duration of recording period | Variable recording periods (1 min to 24 h)                                                                               | 24–48 h during a usual working day (usual physical activity)                                                                                                                                                         |
| Time of measurement          | Variable                                                                                                                 | 24 h/daytime/nighttime<br>Definition of daytime and nighttime intervals using patient's diaries or simultaneous actigraphy recordings<br>Predefine meal and bed times<br>Narrow fixed time intervals also acceptable |
| Stable treatment             | NA                                                                                                                       | Yes                                                                                                                                                                                                                  |
| Advantages                   | Beat-to-beat recordings allow assessment of indices of autonomic cardiovascular modulation                               | Extensive information on 24-h BP profile (nighttime BP dipping, morning surge)<br>Assessment of efficacy of antihypertensive drug treatment over 24 h                                                                |
| Disadvantages                | Stability of measurements might not be guaranteed outside the laboratory setting<br>Possibility of measurement artefacts | ABPM: Cannot be repeated frequently<br>Not well tolerated<br>Not widely available<br>Difficult to standardize subject's behaviour over 24 h                                                                          |

Abbreviations: BP, blood pressure; BPV, blood pressure variations; ABPM, ambulatory blood pressure monitoring.



period of time; and (2) *indices for estimation of specific BPV patterns*, focusing on slower BP variations within 24 hours associated with circadian BP changes (i.e. day/night BP profiles) or with other behavioural factors (i.e. 'siesta'; awakening in the morning). See [Figure 27.2](#).

## INDICES FOR ASSESSMENT OF OVERALL BLOOD PRESSURE VARIABILITY

### INDICES OF DISPERSION

A traditional approach for the estimation of very-short-term BPV when using continuous beat-to-beat BP recordings consists in the calculation of the standard deviation (SD) of each half-hour mean BP value, followed by the calculation of the average of these 48 half-hour SDs ('within half-hour SD') (17). Alternatively, short-term BPV is obtained by calculating the SD of the average of the mean BP values for each of the 48 half hours in which the 24-hour recordings may be subdivided. This other short-term BPV component (the so-called 'among half-hour SD') is thought to reflect slightly slower circadian variations in BP. The first studies implementing these measures showed that short-term BPV increases proportionally to the increase in mean BP levels, being greater during the daytime and during physical activity and lower during the nighttime or during rest (25). These studies also showed that compared to normotensive controls, hypertensive subjects not only have higher mean BP levels but also greater very-short-term BPV (within half-hour SD) and short-term BPV (among half-hour SD) (25). Short-term BPV may also be estimated from noninvasive intermittent 24-hour ABP recordings at intervals from 15 to 20 minutes (22,23) by calculating 24-hour SD, and also the respective SD for the day- and nighttime subperiods (22,25). Although SD represents

the most commonly used index for assessment of BPV and provides a measure of values dispersion over selected time windows (24-hour, day and night), it is affected by trends in BP (e.g. day-night change) and increases with increasing average BP values. To account for such a dependence of SD and other absolute measures of BPV on mean BP levels, the coefficient of variation (CV) ( $SD \times 100 / BP \text{ mean}$ ) may be applied (25). Assessment of global 24-hour SD is significantly influenced by both short-term and day-night BP changes; that is, by components of 24-hour BPV known to have opposite prognostic implications (see following paragraphs). Thus whenever the focus is on short-term BPV over 24 hours, the contribution to overall 24-hour BP SD carried by day-night BP changes has to be identified and removed. This can be achieved through estimation of *weighted 24-hour SD (wSD)* which selectively removes the contribution provided by night time BP fall to 24-hour SD, by weighting daytime and nighttime BP SD for the duration of the day- and nighttime periods, respectively, and by averaging the SD of these two time subperiods (31). The corresponding weighted CV may be calculated as well. *Variability independent of the mean (VIM)* excludes the effect of mean BP on BPV by applying nonlinear regression analysis (i.e. plotting SD against mean) (32). For its estimation, it requires calculation of a factor  $x$  from overall population data (32).

### INDICES OF BPV IN THE FREQUENCY DOMAIN

An accurate estimation of spectral indices for assessment of very-short-term BPV in the frequency domain is only possible from continuous beat-to-beat BP recordings (33). In addition to calculation of SD and other traditional indices of BPV, continuous BP recordings do indeed allow estimation of indices of autonomic cardiovascular modulation by applying power spectral analysis. It decomposes the overall BP variance or

power into its different components oscillating at different frequencies. The corresponding spectral indices are usually obtained by integrating the BP power spectrum over different frequency bands and by focusing on those reported to have a pathophysiological or clinical relevance. This is usually done by computing BP spectral powers over a high-frequency (HF) band (power between 0.15 and 0.50 Hz), a low-frequency (LF) band (power between 0.15 and 0.07 Hz, centred around 0.1 Hz), and a very-low-frequency (VLF) band (power <0.07 Hz). The HF power usually reflects BP changes induced by respiratory mechanics. The LF power mainly quantifies oscillations generated by a resonance in the baroreflex loop, with an important contribution by sympathetic modulation (34). Evidence has been obtained of an adrenergic origin of the VLF powers (35), which may be potentiated in case of autonomic dysfunction by the inability of cardiovascular control mechanisms to 'gate' BP fluctuations around 0.1 Hz, as in the case of arterial baroreceptors or cardiopulmonary receptors denervation in the experimental animal. In addition, alterations in respiratory activity may contribute to the VLF power in pathological conditions like congestive heart failure and obstructive or central sleep apnoea, due to the impact of so-called periodic breathing. Thus spectral BPV indices may yield information on the autonomic control of circulation, on the baroreflex function and on pathological aspects of respiration. Their assessment should be accompanied by assessment of the corresponding heart rate variability spectral powers, which can provide complementary pathophysiologically and clinically relevant information, and by the assessment of respiratory frequency and depth. *Residual variability*, another index of short-term BPV in the frequency domain, may be estimated not only from beat-to-beat continuous BP recordings but also, although less precisely, from intermittent 24-hour ABP recordings at intervals from 15–20 min (22,23). It is computed in the frequency domain through spectral analysis of 24-hour BP fluctuations by assessing the spectral power of faster BP fluctuations remaining in the 24-hour tracing after exclusion of the slower circadian components (first two harmonics) of the 24-hour BP profile.

### INDICES OF SEQUENTIAL BP CHANGES

Average real variability (ARV) is an index of overall variability based on readings sequence. It is computed as the average of the absolute differences between consecutive BP measurements over 24 hours. It focuses on the sequence of BP readings, thus reflecting short-term, reading-to-reading, within-subject variability in BP values (36). ARV has been shown to be a more specific estimate of 24-hour BP variability and a more effective predictor of outcome than SD. Indeed, subjects with different 24-hour ABPM profiles may have similar SD but different ARV (27,36,37). ARV effectively removes the contribution of trends in mean BP to overall BPV and is correlated with mean BP levels. Other indices of overall variability based on reading sequence include *time rate of BP fluctuations* (similar to ARV but quantified as a function of time, to provide information also on speed of BP changes) and *interval-weighted SD* (similar to SD), both of which take into account the interval between measurements, giving greater weight to more distant pairs of readings.

### INDICES OF INSTABILITY

Short-term BP variability may also be assessed by estimation of instability indices that take into account

extreme readings of the distribution of BP values within a given time window such as *range* (maximum–minimum BP), *peak-and-trough values*, *peak size* (maximum–mean BP), and *trough size* (mean–minimum BP). Although some studies have demonstrated their clinical value, a major limitation of these indices is that extreme readings are poorly reliable within a given distribution of values, including ABPM data, especially when focusing on individual subjects, being unstable and prone to show measurement artefacts more than BP values recorded in the usual range.

### INDICES FOR ASSESSMENT OF SPECIFIC PATTERNS OF BLOOD PRESSURE VARIABILITY WITHIN THE 24 HOURS

In addition to estimation of indices of overall variability (which allows assessment of faster BP variations occurring reading to reading over the 24 hours), ambulatory BP recordings also allow estimation of slower fluctuations within the 24 hours associated with circadian BP changes (the day/night cycle) or with other behavioural factors (e.g. 'siesta') (see Figure 27.2). One of the most common among these indices of BPV estimated from 24-hour ABPM is the *nocturnal BP fall*. The reduction in BP during the night can be expressed as percentage of daytime BP [Nocturnal BP fall = (Daytime BP – Nighttime BP)\*100/Daytime BP] which is mathematically equivalent to the night/day ratio. When considering the degree of nocturnal BP fall (dipping) subjects may be classified into four different categories: (1) normal dipping (fall in nighttime systolic and diastolic BP between 10–20%), (2) non-dipping (or more precisely reduced dipping, with a fall in nighttime systolic and diastolic BP <10%), (3) rising or 'inverted dipping' (increase in nighttime BP compared to daytime values), and (4) extreme dipping (BP fall during night >20%) (38). Another index of short-term BPV that can be estimated from 24-hour ABPM when focusing on differences between day and night and which has been suggested to carry a prognostic value is the *morning BP surge* (MBPS). It is computed in different ways, as a function of the different time points set by the researcher to define wake and sleep time periods. The most commonly employed method is the calculation of the difference between the lowest BP value at night and the highest BP value recorded shortly after awakening. However, when computed in this way, it is obvious that correlation with nocturnal BP fall may represent a challenge in the interpretation of its impact on outcome data. Indeed, there are still issues to be defined regarding the best way of computing morning BP surge and its actual clinical value, due to the interference of the degree of nocturnal BP dipping both with morning BP surge estimates and with the assessment of its prognostic value. Other patterns of BP variations that can be evaluated from 24-hour ABPM are the *siesta dipping* (i.e. the BP fall observed in populations where having an afternoon nap, i.e. siesta, is a common habit) and the *postprandial BP fall* (supposedly due to splanchnic vasodilation after a meal which, when excessive, leads to postprandial hypotension and may indicate altered autonomic function). However, to date, no standards have been provided regarding the calculation of these indices.

## CLINICAL RELEVANCE OF SHORT-TERM BLOOD PRESSURE VARIABILITY

The clinical relevance of BPV in the very short and in the short term has been supported by the evidence accumulated in previous decades showing significant associations between these types of BPV with target-organ damage and cardiovascular and mortality outcomes (see Figure 27.1). Most evidence supporting the association of very-short- and short-term BPV with target-organ damage is derived either from cross-sectional studies reporting on such relationship or from prospective studies on the predictive value of BPV regarding the development and progression of target-organ damage (39). Early studies implementing intra-arterial beat-to-beat BP recordings in hypertensive subjects showed that (1) at nearly any level of 24-hour mean BP, the prevalence and severity of target-organ damage was higher in subjects with higher 24-hour BPV (40), and (2) BPV at baseline was a significant predictor of target-organ damage, in particular of left ventricular hypertrophy, at the end of follow-up (41). When considering that short-term BPV as assessed from intermittent ABPM recordings, a recent meta-analysis has shown a significant, although moderate, association between left ventricular mass index and SD of 24-hour systolic BP, SD of daytime systolic BP, wSD of 24-hour systolic BP and ARV of 24-hour systolic BP (with correlation coefficients of 0.22, 0.19, 0.23, 0.37, respectively) (42). Other studies have shown an independent, although moderate, relationship between short-term BPV and carotid atherosclerosis, arterial stiffness and renal function (6,43–45), although not all studies reported significant associations (46,47). In the European Lacidipine Study on Atherosclerosis (ELSA), short-term BPV predicted carotid intima-media thickness by the end of treatment (48), while this was not the case for visit-to-visit BPV (49). Regarding CV outcomes, several studies and analyses of ABPM registries have confirmed the prognostic role of short-term BPV. A recent meta-analysis of observational cohorts and of clinical trials reported significant hazard ratios for cardiovascular events as well as for cardiovascular and all-cause mortality in relation to an increased short-term BPV (50). An analysis of the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) composed of 8,938 subjects (41% hypertension, 48% treated) showed a significant predictive value for short-term BPV for most outcomes, ARV of 24-hour systolic/diastolic ambulatory BP being a better predictor than SD (37). The analysis of the ABPM-International database, composed of 7,112 untreated hypertensive subjects, showed SD of nighttime systolic ambulatory BP to be an independent predictor of cardiovascular events, cardiovascular death, and all-cause mortality in contrast to daytime values, although with a relatively small predicting power, possibly due to the heterogeneity of data collected in different populations with different recording methodology (see below) (51). In the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study, there was an independent relationship between the risk of death and SD of 24-hour, daytime, and nighttime BP (52). Moreover, the adjusted risk of cardiovascular death was inversely related to day-night diastolic BP difference and showed a significant positive relationship with residual diastolic BPV, as computed by spectral powers of 24-hour ABP recordings, after removing the

contribution of the first two harmonics, in particular after removing day-night BP changes (52).

Accumulating evidence suggests that specific patterns of the diurnal BPV may indeed have an important prognostic role. Nighttime ambulatory BP carries superior prognostic value as compared to other BP monitoring methods (53–55). In this context, several studies have investigated whether BP fluctuations occurring from day to night or vice versa may have additional prognostic value. More specifically, a non-dipping and, even more so, a rising pattern at night have been shown to be associated with increased cardiovascular risk, although recent evidence suggests that it is the nighttime average BP level that mainly matters (54). Likewise, an increased morning BP surge is associated with a high incidence of cardiovascular events and mortality, but this should be interpreted in the context of the significant relationship between the degree of morning BP surge (carrying high risk) and the degree of nighttime BP fall (carrying low risk), which may affect calculation of the extent of BP rise in the early morning and the interpretation of its prognostic value (56,57).

Although evidence from some recent studies has indicated an incremental contribution of short-term BPV for cardiovascular risk stratification over and above the impact of average BP values, the relevance of such contribution has been shown to be influenced by the methodology employed for assessment of BPV and by the characteristics and baseline cardiovascular risk of the study populations. While in the ABP-International study the relative integrated discrimination improvement for an increased value of the SD of nighttime systolic BP ranged from 8.5–14.5% for cardiovascular and mortality outcomes (51), in the IDACO analysis, ARV added only 0.1% to prediction of the risk of a composite cardiovascular event (37). It should be mentioned, however, that there were significant differences in the methodology (ambulatory BP readings obtained at 10- to 30-min intervals during daytime and at 15- to 30-min intervals during nighttime versus 15–30 min and 30–60 min, respectively for the ABP-International and IDACO databases) and in the characteristics of the two populations (untreated hypertensives vs. population-based cohorts including treated hypertensives, respectively). Future studies should establish whether there are specific categories (high- vs. low-risk, treated or untreated) of patients where BPV more clearly provides additional predictive information over and above the impact of average BP levels. Although some outcome studies addressing the prognostic value of BPV have suggested reference values and thresholds for BPV, the heterogeneity in the indices of BPV used and the different characteristics of study populations have not provided any definitive recommendation in this regard. An analysis of the ABP-International database showed that a SD of nighttime systolic ambulatory BP  $\geq 12.2$  mmHg (compared with SD  $< 12.2$  mmHg) was associated with greater risk of cardiovascular events (41%), cardiovascular death (55%) and all-cause mortality (59%) (51). The corresponding values for the SD of diastolic BP  $\geq 7.9$  mmHg were 48%, 132% and 77% (51). The IDACO analysis also presented the risk of total and cardiovascular mortality by fifths of distribution of ARV showing progressively increased risk among quartiles with higher event rate at systolic/diastolic ARV values of 16.2/12.4 mmHg, respectively (37). In recent years, a series of studies or *post hoc* analyses of clinical trials in hypertension have also



addressed the important issue of whether there are drugs able to specifically reduce BPV and whether such reduction is translated into an improved cardiovascular risk. In the NatriLix SR versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) Study, the effect of different antihypertensive agents (candesartan, indapamide sustained release and amlodipine) on ambulatory BPV was examined. Amlodipine and indapamide were the only agents associated with a significantly decreased ambulatory BPV after a 3-month treatment (58). In another study in 2780 hypertensive subjects, it was shown that those treated with calcium channel blockers or diuretics alone, or in addition to other drugs, had significantly lower SD of 24-hour systolic BP compared with those not treated with these classes (59).

Current antihypertensive treatment often consists of once-daily administration of long-acting antihypertensive drugs upon awakening. Since the vast majority of drugs have a trough-to-peak ratio lower than 100%, it is expected that a diminished effect occurs during nighttime and the early morning hours of the next day. This phenomenon may have important implications for subjects with nighttime hypertension and/or non-dipping profile and/or pronounced morning surge. Preliminary results derived from a single research centre in Spain (MAPEC study) appear to support bedtime dosing of at least one of the antihypertensive drugs in terms of cardiovascular prognosis (60). However, the findings of this particular study and the concept of restoring a disturbed nighttime BP profile with the so called 'chronotherapy' need to be confirmed by other groups. In general, more evidence is needed before recommending BPV as a possible target for treatment and before suggesting selection of any specific treatment in this regard, if not general advice on use of long-lasting drugs and drug combinations to smooth a 24-hour BP profile.

## CONCLUSIONS

BP variations occurring over 24 hours may be evaluated in the very short term through beat-by-beat continuous BP recordings, or in the short term by using 24-hour ABPM, which allows evaluation of either faster short-term BPV (i.e. reading-by-reading BP changes over 24 hours) or slower BPV (i.e. BP changes associated with circadian rhythms or with behavioural factors). Although in physiological conditions, short-term BP variations may represent a response of intrinsic cardiovascular regulatory mechanisms to external environmental, behavioural or emotional stimuli from daily life, they may also reflect alterations in mechanisms responsible for cardiovascular homeostasis or the presence of underlying pathological conditions associated with autonomic dysfunction. Increasing values of overall short-term BPV or alterations in different patterns of BPV (i.e. impaired day-to-night BP profiles) are associated with development, progression and severity of cardiac, vascular and renal organ damage and with an increased risk of cardiovascular events and cardiovascular and all-cause mortality, supporting the concept that short-term BPV may contribute to cardiovascular risk prediction over and above the impact of average BP levels. These findings suggest the possible usefulness

of assessing BPV in clinical practice and of considering an elevated BPV as a possible target for treatment to further improve prognosis. However, currently available studies are characterized by a significant heterogeneity in the methodology applied for estimating BPV indices, and although many indices of short-term BPV have been shown to be of prognostic value, no interventional longitudinal outcome study has yet been conducted specifically addressing what short-term BPV levels should be regarded as normal, and what short-term BPV level should be achieved as target for antihypertensive treatment. Similarly, no intervention study has yet explored the key question of whether a reduction in short-term BPV by treatment translates into a better outcome.

## REFERENCES

1. Mancia G, Parati G, Pomidossi G et al. Arterial baroreflexes and blood pressure and heart rate variabilities in humans. *Hypertension* 1986; 8(2): 147–153.
2. Parati G, Saul JP, Di Rienzo M, Mancia G. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation. A critical appraisal. *Hypertension* 1995; 25(6): 1276–1286.
3. Narkiewicz K, Winnicki M, Schroeder K et al. Relationship between muscle sympathetic nerve activity and diurnal blood pressure profile. *Hypertension* 2002; 39(1): 168–172.
4. Parati G, Faini A, Valentini M. Blood pressure variability: Its measurement and significance in hypertension. *Curr Hypertens Rep* 2006; 8(3): 199–204.
5. Kotsis V, Stabouli S, Karafilis I et al. Arterial stiffness and 24 h ambulatory blood pressure monitoring in young healthy volunteers: The early vascular ageing Aristotle University Thessaloniki Study (EVA-ARIS Study). *Atherosclerosis* 2011; 219(1): 194–199.
6. Schillaci G, Bilo G, Pucci G et al. Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: Findings from 2 large databases. *Hypertension* 2012; 60(2): 369–377.
7. Okada H, Fukui M, Tanaka M et al. Visit-to-visit variability in systolic blood pressure is correlated with diabetic nephropathy and atherosclerosis in patients with type 2 diabetes. *Atherosclerosis* 2012; 220(1): 155–159.
8. Noll G, Wenzel RR, Schneider M et al. Increased activation of sympathetic nervous system and endothelin by mental stress in normotensive offspring of hypertensive parents. *Circulation* 1996; 93(5): 866–869.
9. Grassi G, Seravalle G, Quarti-Trevano F et al. Adrenergic, metabolic, and reflex abnormalities in reverse and extreme dipper hypertensives. *Hypertension* 2008; 52(5): 925–931.
10. Fujii T, Uzu T, Nishimura M et al. Circadian rhythm of natriuresis is disturbed in nondipper type of essential hypertension. *Am J Kidney Dis* 1999; 33(1): 29–35.
11. Verdecchia P, Schillaci G, Gatteschi C et al. Blunted nocturnal fall in blood pressure in hypertensive women with future cardiovascular morbid events. *Circulation* 1993; 88(3): 986–992.
12. Haynes WG. Role of leptin in obesity-related hypertension. *Exp Physiol* 2005; 90(5): 683–688.
13. Quinaglia T, Martins LC, Figueiredo VN et al. Non-dipping pattern relates to endothelial dysfunction in patients with uncontrolled resistant hypertension. *J Hum Hypertens* 2011; 25(11): 656–664.
14. Holt-Lunstad J, Steffen PR. Diurnal cortisol variation is associated with nocturnal blood pressure dipping. *Psychosom Med* 2007; 69(4): 339–343.
15. Panarelli M, Terzolo M, Piovesan A et al. 24-hour profiles of blood pressure and heart rate in Cushing's syndrome. Evidence for differential control of cardiovascular variables by glucocorticoids. *Ann Ital Med Int* 1990; 5(1): 18–25.
16. Bevan A, Stott FH. Portable recorder for continuous arterial pressure measurement in man. *J Physiol* 1966; 38: 186–190.
17. Mancia G, Ferrari A, Gregorini L et al. Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. *Circ Res* 1983; 53(1): 96–104.
18. Penaz J. Current photoelectric recording of blood flow through the finger. *Cesk Fysiol* 1975; 24(4): 349–352.



19. Smith NT, Wesseling KH, de Wit B. Evaluation of two prototype devices producing noninvasive, pulsatile, calibrated blood pressure measurement from a finger. *J Clin Monit* 1985; 1(1): 17–29.
20. Parati G, Casadei R, Groppelli A et al. Comparison of finger and intra-arterial blood pressure monitoring at rest and during laboratory testing. *Hypertension* 1989; 13(6 Pt 1): 647–655.
21. Imholz BP, Langewouters GJ, van Montfrans GA et al. Feasibility of ambulatory, continuous 24-hour finger arterial pressure recording. *Hypertension* 1993; 21(1): 65–73.
22. Mancia G, Di Rienzo M, Parati G. Ambulatory blood pressure monitoring use in hypertension research and clinical practice. *Hypertension* 1993; 21(4): 510–524.
23. Parati G, Ochoa JE, Bilo G. Blood pressure variability, cardiovascular risk, and risk for renal disease progression. *Curr Hypertens Rep* 2012; 14(5): 421–431.
24. Parati G, Stergiou G, O'Brien E et al. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. *J Hypertens* 2014; 32(7): 1359–1366.
25. di Rienzo M, Grassi G, Pedotti A, Mancia G. Continuous vs intermittent blood pressure measurements in estimating 24-hour average blood pressure. *Hypertension* 1983; 5(2): 264–269.
26. Booth JN III, Muntner P, Abdalla M et al. Differences in night-time and daytime ambulatory blood pressure when diurnal periods are defined by self-report, fixed-times, and actigraphy: Improving the Detection of Hypertension study. *J Hypertens* 2016; 34(2): 235–243.
27. O'Brien E, Parati G, Stergiou G et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens* 2013; 31(9): 1731–1768.
28. Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31(7): 1281–1357.
29. Stergiou GS, Parati G, Vlachopoulos C et al. Methodology and technology for peripheral and central blood pressure and blood pressure variability measurement: Current status and future directions - Position statement of the European Society of Hypertension Working Group on blood pressure monitoring and cardiovascular variability. *J Hypertens* 2016; 34(9): 1665–1677.
30. Parati G, Stergiou GS, Asmar R et al. European Society of Hypertension guidelines for blood pressure monitoring at home: A summary report of the Second International Consensus Conference on Home Blood Pressure Monitoring. *J Hypertens* 2008; 26(8): 1505–1526.
31. Bilo G, Giglio A, Styczkiewicz K et al. A new method for assessing 24-h blood pressure variability after excluding the contribution of nocturnal blood pressure fall. *J Hypertens* 2007; 25(10): 2058–2066.
32. Rothwell PM, Howard SC, Dolan E et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 2010; 375(9718): 895–905.
33. Mancia G PG, di Rienzo M, Zanchetti A. Blood pressure variability. In: Mancia G ZA (ed). *Handbook of Hypertension: Pathophysiology of Hypertension*. Amsterdam: Elsevier Science; 1997: 117–169.
34. Di Rienzo M, Castiglioni P, Parati G et al. Baroreflex modulation of the cardiovascular system: New insights from the joint analysis of blood pressure and heart rate signals. *Technol Health Care* 1996; 4(1): 121–128.
35. Radaelli A, Castiglioni P, Centola M et al. Adrenergic origin of very low-frequency blood pressure oscillations in the unanesthetized rat. *Am J Physiol Heart Circ Physiol* 2006; 290(1): H357–H364.
36. Mena L, Pintos S, Queipo NV et al. A reliable index for the prognostic significance of blood pressure variability. *J Hypertens* 2005; 23(3): 505–511.
37. Hansen TW, Thijs L, Li Y et al. Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. *Hypertension* 2010; 55(4): 1049–1057.
38. Pickering TG, Hall JE, Appel LJ et al. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: Blood pressure measurement in humans: A statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* 2005; 45(1): 142–161.
39. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. *Nat Rev Cardiol* 2013; 10(3): 143–155.
40. Parati G, Pomidossi G, Albini F et al. Relationship of 24-hour blood pressure mean and variability to severity of target-organ damage in hypertension. *J Hypertens* 1987; 5(1): 93–98.
41. Frattola A, Parati G, Cuspidi C et al. Prognostic value of 24-hour blood pressure variability. *J Hypertens* 1993; 11(10): 1133–1137.
42. Madden JM, O'Flynn AM, Fitzgerald AP, Kearney PM. Correlation between short-term blood pressure variability and left-ventricular mass index: A meta-analysis. *Hypertens Res* 2016; 39(3): 171–177.
43. Shintani Y, Kikuya M, Hara A et al. Ambulatory blood pressure, blood pressure variability and the prevalence of carotid artery alteration: The Ohasama study. *J Hypertens* 2007; 25(8): 1704–1710.
44. Tatasciore A, Renda G, Zimarino M et al. Awake systolic blood pressure variability correlates with target-organ damage in hypertensive subjects. *Hypertension* 2007; 50(2): 325–332.
45. Manios E, Tsagalis G, Tsivgoulis G et al. Time rate of blood pressure variation is associated with impaired renal function in hypertensive patients. *J Hypertens* 2009; 27(11): 2244–2248.
46. Veloudi P, Blizzard CL, Head GA et al. Blood pressure variability and prediction of target organ damage in patients with uncomplicated hypertension. *Am J Hypertens* 2016; 29(9): 1046–1054.
47. Wei FF, Li Y, Zhang L et al. Beat-to-beat, reading-to-reading, and day-to-day blood pressure variability in relation to organ damage in untreated Chinese. *Hypertension* 2014; 63(4): 790–796.
48. Mancia G, Parati G, Hennig M et al. Relation between blood pressure variability and carotid artery damage in hypertension: Baseline data from the European Lacidipine Study on Atherosclerosis (ELSA). *J Hypertens* 2001; 19(11): 1981–1989.
49. Mancia G, Facchetti R, Parati G, Zanchetti A. Visit-to-visit blood pressure variability, carotid atherosclerosis, and cardiovascular events in the European Lacidipine Study on Atherosclerosis. *Circulation* 2012; 126(5): 569–578.
50. Stevens SL, Wood S, Koshiaris C et al. Blood pressure variability and cardiovascular disease: Systematic review and meta-analysis. *BMJ* 2016; 354: i4098.
51. Palatini P, Reboli G, Beilin LJ et al. Added predictive value of night-time blood pressure variability for cardiovascular events and mortality: The Ambulatory Blood Pressure-International Study. *Hypertension* 2014; 64(3): 487–493.
52. Mancia G, Bombelli M, Facchetti R et al. Long-term prognostic value of blood pressure variability in the general population: Results of the Pressioni Arteriose Monitorate e Loro Associazioni Study. *Hypertension* 2007; 49(6): 1265–1270.
53. Niiranen TJ, Maki J, Puukka P et al. Office, home, and ambulatory blood pressures as predictors of cardiovascular risk. *Hypertension* 2014; 64(2): 281–286.
54. Hansen TW, Li Y, Boggia J et al. Predictive role of the nighttime blood pressure. *Hypertension* 2011; 57(1): 3–10.
55. Fagard RH, Celis H, Thijs L et al. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension* 2008; 51(1): 55–61.
56. Metoki H, Ohkubo T, Kikuya M et al. Prognostic significance for stroke of a morning pressor surge and a nocturnal blood pressure decline: The Ohasama study. *Hypertension* 2006; 47(2): 149–154.
57. Kario K, Pickering TG, Umeda Y et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: A prospective study. *Circulation* 2003; 107(10): 1401–1406.
58. Zhang Y, Agnoletti D, Safar ME, Blacher J. Effect of antihypertensive agents on blood pressure variability: The NatriX SR versus candesartan and amlodipine in the reduction of systolic blood pressure in hypertensive patients (X-CELLENT) study. *Hypertension* 2011; 58(2): 155–160.
59. Levi-Marpillat N, Macquin-Mavier I, Tropeano AI et al. Antihypertensive drug classes have different effects on short-term blood pressure variability in essential hypertension. *Hypertens Res* 2014; 37(6): 585–590.
60. Hermida RC, Ayala DE, Mojon A, Fernandez JR. Influence of circadian time of hypertension treatment on cardiovascular risk: Results of the MAPEC study. *Chronobiol Int* 2010; 27(8): 1629–1651.

# EXERCISE BLOOD PRESSURE: THE PROGNOSTIC IMPACT OF EXERCISE SYSTOLIC BLOOD PRESSURE

# 28

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## INTRODUCTION

It was recognized at the beginning of the twentieth century that blood pressure measurements during or shortly after physical exercise might provide valuable information about the cardiovascular system. Gordon Lambert described the value of exercise blood pressure measurements as well as some of the most important controversies and difficulties in 1918 (1). Lambert pointed out that reliable diastolic blood pressure measurements during exercise were difficult to obtain, and thus he only emphasized the systolic blood pressure levels. Despite more than a century of research on exercise blood pressure, no consensus has been established on which blood pressure levels represent a normal response to exercise of a given intensity.

## EXERCISE HYPOTENSION

A drop in or an inability to increase blood pressure during exercise from pre-exercise values has been recognized as a reason for termination of exercise tests for decades, and represents an inability to adapt to the physiological stressor made by exercise. No consensus exists on the blood pressure thresholds defining exercise hypotension, but a drop in systolic blood pressure below pre-exercise values has often been used. The aetiology of exercise hypotension is multifactorial and indicative of underlying cardiovascular disease, and in patients with established cardiovascular disease it is a marker of poor prognosis (2–5).

## EXAGGERATED BLOOD PRESSURE RESPONSE TO PHYSICAL EXERCISE

A hypertensive response to exercise at moderate workload is associated with future risk of cardiovascular disease and mortality (6–8). However, some studies have shown conflicting results, and the results can potentially also be cancelled out by resting systolic blood pressure (7,9). Reasons for this may be several methodological differences and

considerations, as well as absent evidence regarding the importance of exercise blood pressure.

## IMPORTANCE OF AN EXAGGERATED BLOOD PRESSURE RESPONSE TO PHYSICAL EXERCISE

Fagard et al. performed one of the earliest studies on exercise blood pressure and cardiovascular outcome in a strict protocol using intra-arterial blood pressure measurement (9). Their results showed a significant correlation between exercise blood pressure and both cardiovascular events and total mortality, but not independent of resting blood pressure. However, the 143 participants who were included were under treatment or assessment for hypertension, and some were also beginning to show signs of end-organ damage. The follow-up time was limited to an average of 11 years, and the highest workload achieved by all participant was 50W, indicating a rather low minimum cardiorespiratory fitness in the cohort. The following year, Filipovsky et al. published their study, possibly the first long-term follow-up aiming to assess the predictive value of exercise blood pressure (6). With more than 4900 participants followed for on average 17 years and excluding participants with severe hypertension or under antihypertensive treatment, they found that the increase in exercise systolic blood pressure was associated with cardiovascular mortality in a Cox regression model adjusting for age, smoking, total cholesterol, body mass index, left ventricular hypertrophy on ECG, sports activity and systolic blood pressure and heart rate at rest. Weiss et al. investigated a cohort of more than 6500 participants, including 45% women, and found no significantly increased risk of cardiovascular mortality with increased exercise blood pressure during treadmill test using the Bruce protocol in the overall analysis (7). Interestingly, when performing subgroup analyses on participants without established hypertension, they found an increase in cardiovascular mortality risk independent of both systolic and diastolic blood pressure at rest measured at Bruce stage 2. These

results indicated an ability of exercise blood pressure at moderate workload to provide early prognostic information in patients without hypertension. The predictive value of exercise blood pressure seemed to be attenuated in the presence of hypertension, and most likely also end-organ damage.

The Oslo Ischemia Study cohort is to our knowledge the only cohort that has been followed with repeated exercise tests over several years, according to a highly standardised protocol (10) and with long-term follow-up. The Oslo Ischemia Study included 2014 initially healthy men aged 40–59 years and has provided several publications on the prognostic value of exercise blood pressure regarding cardiovascular disease. Participants had to perform a symptom-limited, ECG-monitored bicycle test starting at a workload of 100W, equal to 600 kilopondmeter (kpm)/min or 5.5 metabolic equivalents (METs). The test was performed on an electrically braked stationary bicycle with ergometer. After the initial 6 minutes, the workload was increased with 50W every sixth minute. The participants were encouraged to continue exercising until near exhaustion or objective signs of cardiac ischemia appeared on ECG.

Results from this cohort have previously shown that systolic blood pressure at the moderate workload of 100W predicts coronary heart disease and cardiovascular mortality in apparently healthy, middle-aged, Caucasian men after 16 years of follow-up (10,11). The risk of cardiovascular mortality was independent of resting systolic blood pressure after 21 years of follow-up (12). In the same cohort, a temporal increase in exercise systolic blood pressure over 7 years has also been reported to predict long-term risk of coronary heart disease and mortality (13). The results remained robust and significant for exercise systolic blood pressure on cardiovascular mortality when extending the follow-up from 21 years to 35 years (14,15). Participants

were divided into quartiles based on peak systolic blood pressure at 100W, and the risk of cardiovascular mortality increased more than threefold in the highest quartile (200–270 mmHg,  $n = 489$ ) compared to the lowest quartile (100–160 mmHg,  $n = 457$ ). When adjusting for classical cardiovascular risk factors, there was still a 1.5-fold increased risk of cardiovascular mortality in the highest quartile compared to the lowest quartile (Figure 28.1). Additional adjustments for physical fitness had minor impact on the association. There was also a significantly and independently increased risk of cardiovascular mortality when comparing the third quartile (180–195 mmHg,  $n = 545$ ) to the lowest quartile.

The risk of cardiovascular disease (fatal or nonfatal myocardial infarction; angina pectoris; heart failure; fatal or nonfatal stroke, either haemorrhagic or ischaemic; transient ischaemic attack; abdominal aortic aneurysm; peripheral artery disease and claudicatio intermittens) also showed a significant and independent association with systolic blood pressure at 100 W after 35 years of follow-up (Figure 28.2).

The finding of a significant association between exercise systolic blood pressure and cardiovascular mortality is consistent with our previous findings from this cohort and a recent meta-analysis and reviews regarding exercise systolic blood pressure (5,8). It is our opinion that increased exercise systolic blood pressure should be regarded as a consistent and reliable predictor for cardiovascular mortality. The association for cardiovascular disease is not as strong compared with cardiovascular mortality, and the results are cancelled out in the multivariate analysis by physical fitness (14). Nonetheless, the results of this study indicate that exercise systolic blood pressure predicts cardiovascular disease independent of the classical cardiovascular risk factors. One reason explaining the different predictive power of exercise

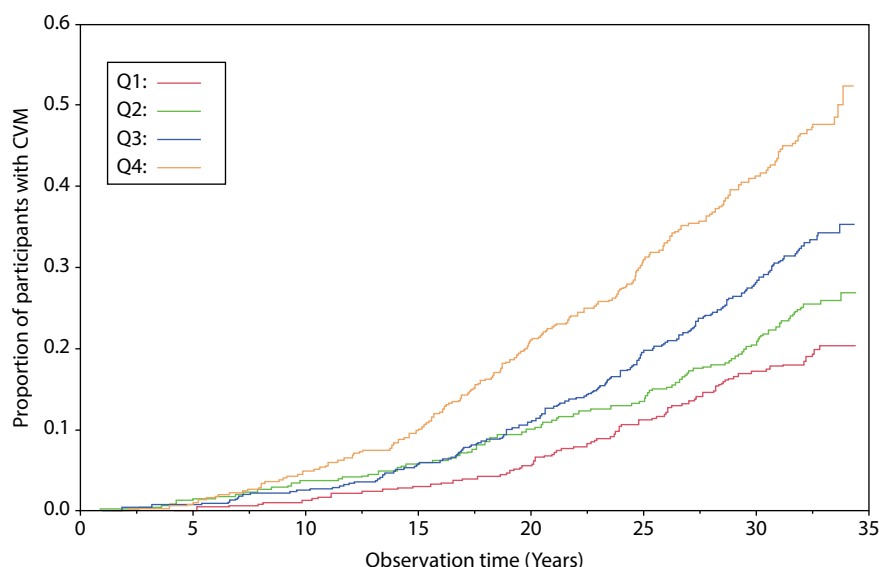


**Figure 28.1** Kaplan-Meier plot showing cardiovascular mortality (CVM) after 35 years in participants divided into quartiles of SBP100W, Q1 (100–160 mmHg, red plot), Q2 (165–175 mmHg, green plot), Q3 (180–195 mmHg, blue plot) and Q4 ( $\geq 200$  mmHg, orange plot).  $N = 1999$ . CVM includes fatal myocardial infarction, stroke, ruptured aortic aneurysm and sudden death. (From Mariampillai JE et al. *Blood Press* 2017; 26: 229–236. With permission.)

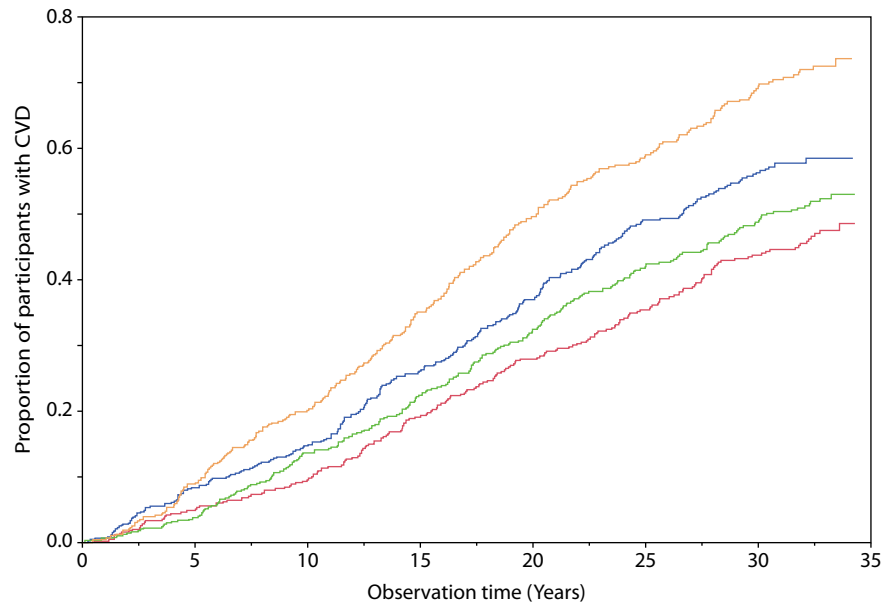


**Figure 28.2** Kaplan-Meier plot showing cardiovascular disease (CVD) after 35 years in participants divided into quartiles of SBP100W, Q1 (100–160 mmHg, red plot), Q2 (165–175 mmHg, green plot), Q3 (180–195 mmHg, blue plot) and Q4 ( $\geq 200$  mmHg, orange plot).  $N = 1999$ . Cardiovascular disease includes peripheral artery disease, abdominal aortic aneurysm, claudicatio intermittens, fatal or nonfatal cerebral stroke, transient ischaemic attack, angina pectoris, fatal or nonfatal myocardial infarction and heart failure. Abbreviation: CVD, cardiovascular disease. (From Mariampillai JE et al. *Blood Press* 2017; 26: 229–236. With permission.)

systolic blood pressure regarding cardiovascular mortality and cardiovascular disease might be that the latter group contains ‘softer’ endpoints as angina pectoris and intermittent claudication, possibly attenuating the results. It is also possible that elevated systolic blood pressure during exercise is a more potent inducer of atherosclerosis in coronary and cerebral arteries, favouring cardiovascular mortality rather than cardiovascular disease including peripheral artery disease.

The risk of cardiovascular disease seems also to be present at lower exercise systolic blood pressure. When performing stepwise analyses comparing sustained elevation of exercise blood pressure to exercise blood pressure persistently below incremental threshold values between 160–195 mmHg, it seems that there is an increased cardiovascular risk already at 165 mmHg, independent of both resting systolic blood pressure and physical fitness (16).

In the recent studies of exercise blood pressure from the Oslo Ischemia Study cohort, physical fitness and family history of coronary heart disease have been included in the multivariate analyses, both being quite unusual adjustment variables in epidemiological analyses. The rationale for performing adjustments for physical fitness at maximal workload is that participants have different physical capacity, and even though the exercise systolic blood pressure is measured at moderate workload, this workload also represents different levels of the participants’ total capacity. Regarding family history of coronary heart disease, heritage is one of the most powerful predictors for cardiovascular disease. The results from our study are also altered little when adding further adjustments in a model including the classical cardiovascular risk factors and family history. Most of the adjustments are therefore covered

by heritage, hence justifying including the parameter in the multivariate analyses.

## PHYSIOLOGY AND PATHOPHYSIOLOGY RELATED TO EXERCISE SYSTOLIC BLOOD PRESSURE

During exercise, an increase in systolic blood pressure is considered to be a normal physiological response. The hemodynamic changes are due to the increase in cardiac output needed to meet the metabolic demands of the exercising muscles, and roughly, systolic blood pressure increases with increasing workload. Why some individuals show an exaggerated systolic exercise blood pressure during exercise is not fully understood. The aetiology is most likely of vascular origin rather than due to left ventricular hypertrophy and dysfunction, as often seen in exercise-induced hypotension (4). Insufficient reduction in total peripheral resistance due to failing vascular properties and/or endothelial dysfunction has been proposed (4,17,18). The exercise protocol in the Oslo Ischemia Study was used by some of the authors of this paper, showing a significantly higher total peripheral vascular resistance in men with exercise systolic blood pressure  $\geq 200$  mmHg (18).

It is not possible to determine the pathophysiological mechanism for the association between exercise systolic blood pressure and cardiovascular disease or mortality in epidemiological studies. Therefore, exercise systolic blood pressure might act as a marker for a yet unknown, or possibly



a known (18), but not acknowledged, risk factor for cardiovascular disease and mortality. In subjects without hypertension at rest, exercise blood pressure has been shown to correlate to blood pressure responses during physical stress in daily life (19), and consequently also associations with increased risk of future cardiovascular disease not discovered by blood pressure measurements after 5 minutes of rest in supine or sitting position. Among individuals demonstrating an exaggerated systolic blood pressure response to exercise, both at maximal- or low-intensity effort, there is a greater prevalence of masked hypertension, which to some degree might explain the increased risk of cardiovascular mortality (20). Another possibility is that moderate workload represents a physiological stressor, revealing failing compensatory mechanisms not discovered under standardised resting conditions, e.g. early vascular stiffness or exaggerated sympathetic response. Even though 100W is to be considered as a moderate workload, the shift from rest to exercise without a more gradual increase in workload may enhance the effect on blood pressure. If so, elevated exercise systolic blood pressure must be regarded as a marker of disease rather than a risk factor for developing disease, as has been emphasized earlier (11).

### EXERCISE SYSTOLIC BLOOD PRESSURE AT DIFFERENT WORKLOADS AND IMPACT OF PHYSICAL FITNESS

During the exercise test, systolic blood pressure is most often measured at several different intensities or workloads. If exercise systolic blood pressure is associated with cardiovascular disease and mortality, it is reasonable to believe that peak systolic blood pressure would have an impact on risk prediction. In the recent reports from the Oslo Ischemia Study, none of the results are altered by peak systolic blood pressure, and systolic blood pressure at moderate workload seems to provide the important prognostic information. This is consistent with other studies, both from this cohort and other studies investigating exercise systolic blood pressure, including systematic reviews and meta-analysis by Schultz et al. (8,12), but differs from research on stroke from the Oslo Ischemia Study (21). Prestgaard et al. found that maximal systolic blood pressure during exercise predicts long-term risk of stroke and discusses the possibility that cerebral arteries are more susceptible to spikes in blood pressure, and thereby are prone to earlier development of disease than coronary arteries. The meta-analysis by Schultz et al. is the first of its kind and shows a 4% increase in cardiovascular risk per 10 mmHg increase in exercise systolic blood pressure when comprising more than 46,000 patients followed for a mean of 15 years. For maximal systolic blood pressure, there was no significant association with cardiovascular events. One might speculate on why peak systolic blood pressure during exercise is cancelled out by other predictors in most studies on cardiovascular events. One reason is that peak systolic blood pressure is dependent on duration and workload of exercise. This to a great extent depends on how much effort each participant puts into the test, which is based on subjective qualities differing between participants. In addition to difficulties reaching the proper

workload representing maximal workload, greater effort might cause greater movement artefacts and disturbances which could result in unreliable values, at least when using a noninvasive method. Diastolic blood pressure or pulse pressure is often not investigated in exercise studies due to difficulties obtaining reliable results in an exercise setting with noninvasive measurements.

Because maximum exercise capacity differs between participants, adjustment for physical fitness in addition to the classical cardiovascular risk factors is important. Although 100W is considered to be a moderate workload, some participants may show a physiologically increased systolic blood pressure due to being closer to their maximum exercise capacity. This is reflected by the alterations in the results when introducing physical fitness in the multivariate model. In addition, exaggerated blood pressure in athletes with high cardiorespiratory fitness does not seem to have the same impact on end-organ damage and is thus unlikely to represent the same impact on cardiovascular risk (5). Adjustments for physical fitness should therefore be mandatory when studying the importance of systolic blood pressure levels at low-to-moderate intensity.

The importance of an exaggerated blood pressure response to physical exercise is likely to be equal among men and women (7,8), even though different gender-specific cutoff values for exercise blood pressure may exist.

### CLINICAL ASPECTS OF EXAGGERATED EXERCISE SYSTOLIC BLOOD PRESSURE

There is no agreement on what should be considered to be an inappropriate or exaggerated systolic blood pressure response to exercise, and the threshold values have only been arbitrarily defined (4). Some studies have used the 90th or 95th percentile, or systolic blood pressure  $\geq 210$  mmHg for men and systolic blood pressure  $\geq 190$  mmHg for women (22–24). Based on the findings in our studies, a larger proportion of the population might have an increased risk of cardiovascular disease and mortality than earlier acknowledged by using the arbitrarily defined limits referred to above.

Exercise systolic blood pressure measurements are of uncertain clinical importance until threshold values for exercise systolic blood pressure are defined. It is not known if intervention alters outcome in individuals with hypertensive response to exercise (19). Still, with the predictive power of exercise systolic blood pressure, exercise systolic blood pressure might be used in the overall risk assessment of individuals and in the future help clinicians decide which individuals would benefit from regular examinations and invasive, pharmacological or lifestyle interventions. The discovery of exercise-induced hypertension should at least lead to extensive assessment of masked hypertension and pre-hypertension with standard office blood pressure measurement and ambulatory blood pressure measurement, and treatment according to guidelines if hypertension is revealed, as recommended by current European hypertension guidelines (25).

Several aspects remain to be clarified regarding exercise blood pressure and its prognostic impact on cardiovascular risk estimation and before its implementation in clinical practice. The research on exercise blood pressure



is based on multiple exercise protocols and methods for performing exercise, e.g. treadmill or bicycle tests. It seems that exercise tests with a moderate starting workload and steady increments challenging enough to be an adequate stressor on the patient's physiology, thereby inducing a sufficient blood pressure increase, are necessary to predict independent risk. One might also speculate on whether a bicycle test is better than treadmill tests, as the performance to a greater extent might be limited by cardiorespiratory fitness rather than musculoskeletal conditions. The pathophysiological mechanisms behind exaggerated exercise blood pressure also need to be scrutinised. The causes of hypertension are in most cases unknown, and the reasons for high exercise blood pressure may not be less complex in nature. The most important aspect, though, is what to do with 'exercise hypertension', and clinical trials investigating the effect of intervention on exaggerated exercise blood pressure are encouraged.

### CONCLUSION REGARDING PROGNOSTIC IMPACT OF EXERCISE BLOOD PRESSURE

The prognostic impact of a hypotensive response to exercise is well established and seems uncontroversial. Often, this response is caused by serious underlying cardiovascular disease and should lead to a thorough cardiovascular assessment.

Current evidence has revealed a reliable association between an exaggerated systolic blood pressure response to exercise testing at moderate or submaximal intensity and increased risk of future cardiovascular disease. The association seems to be independent of resting systolic blood pressure. The possible association between systolic blood pressure at maximal exercise intensity and cardiovascular risk is to some extent conflicting, but current evidence indicates that an exaggerated blood pressure response at maximal intensity often indicates established or future hypertension and thereby increased cardiovascular risk. An exaggerated exercise blood pressure response should be considered to be an independent predictor of cardiovascular risk and masked or future hypertension, which in turn should lower the threshold for antihypertensive treatment strategies.

In order to further clarify the prognostic and diagnostic value of exercise blood pressure, there is urgent need to agree on standardised exercise protocols and measurements; and to reach consensus on what a normal blood pressure response during exercise is, and also use this in clinical, interventional trials.

### REFERENCES

1. Lambert G. The exercise blood pressure test of myocardial efficiency. *BMJ* 1918; 2: 366–368.
2. Dubach P, Froelicher VF, Klein J et al. Exercise-induced hypotension in a male population. Criteria, causes, and prognosis. *Circulation* 1988; 78: 1380–1387.
3. O'Neal WT, Qureshi WT, Blaha MJ et al. Systolic blood pressure response during exercise stress testing: The Henry Ford Exercise Testing (FIT) Project. *J Am Heart Assoc* 2015; 4(5): pii: e002050.
4. Le VV, Mitiku T, Sungar G et al. The blood pressure response to dynamic exercise testing: A systematic review. *Prog Cardiovasc Dis* 2008; 51: 135–160.
5. Schultz MG, La Gerche A, Sharman JE. Blood pressure response to exercise and cardiovascular disease. *Curr Hypertens Rep* 2017; 19: 89.
6. Filipovsky J, Ducimetiere P, Safar ME. Prognostic significance of exercise blood pressure and heart rate in middle-aged men. *Hypertension* 1992; 20: 333–339.
7. Weiss SA, Blumenthal RS, Sharrett AR et al. Exercise blood pressure and future cardiovascular death in asymptomatic individuals. *Circulation* 2010; 121: 2109–2116.
8. Schultz MG, Otahal P, Cleland VJ et al. Exercise-induced hypertension, cardiovascular events, and mortality in patients undergoing exercise stress testing: A systematic review and meta-analysis. *Am J Hypertens* 2013; 26: 357–366.
9. Fagard R, Staessen J, Thijs L, Amery A. Prognostic significance of exercise versus resting blood pressure in hypertensive men. *Hypertension* 1991; 17: 574–578.
10. Mundal R, Kjeldsen SE, Sandvik L et al. Exercise blood pressure predicts cardiovascular mortality in middle-aged men. *Hypertension* 1994; 24: 56–62.
11. Mundal R, Kjeldsen SE, Sandvik L et al. Exercise blood pressure predicts mortality from myocardial infarction. *Hypertension* 1996; 27: 324–329.
12. Kjeldsen SE, Mundal R, Sandvik L et al. Supine and exercise systolic blood pressure predict cardiovascular death in middle-aged men. *J Hypertens* 2001; 19: 1343–1348.
13. Skretteberg PT, Grundvold I, Kjeldsen SE et al. Seven-year increase in exercise systolic blood pressure at moderate workload predicts long-term risk of coronary heart disease and mortality in healthy middle-aged men. *Hypertension* 2013; 61: 1134–1140.
14. Mariampillai JE, Engeseth K, Kjeldsen SE et al. Exercise systolic blood pressure at moderate workload predicts cardiovascular disease and mortality through 35 years of follow-up in healthy, middle-aged men. *Blood Press* 2017; 26: 229–236.
15. Skretteberg PT, Grundvold I, Kjeldsen SE et al. Exercise systolic blood pressure at 100 watt predicts cardiovascular mortality in apparently healthy men; a 35-year follow-up study. *J Hypertens* 2010; 28(e-Suppl): e405.
16. Mariampillai JE, Engeseth K, Kjeldsen SE et al. Exercise blood pressure at moderate workload: Which threshold level predicts coronary heart disease in healthy, middle-aged men? 27th Annual Meeting on Hypertension and Cardiovascular Protection. *J Hypertens* 2017; 35(e-Suppl.2): e30.
17. Chang HJ, Chung J, Choi SY et al. Endothelial dysfunction in patients with exaggerated blood pressure response during treadmill test. *Clin Cardiol* 2004; 27: 421–425.
18. Fossum E, Hoieggan A, Moan A et al. Insulin sensitivity is related to physical fitness and exercise blood pressure to structural vascular properties in young men. *Hypertension* 1999; 33: 781–786.
19. Laukkanen JA, Kurl S. Blood pressure responses during exercise testing - is up best for prognosis? *Ann Med* 2012; 44: 218–224.
20. Sharman JE, Hare JL, Thomas S et al. Association of masked hypertension and left ventricular remodeling with the hypertensive response to exercise. *Am J Hypertens* 2011; 24: 898–903.
21. Prestgaard E, Hodnesdal C, Engeseth K et al. Long-term predictors of stroke in healthy middle-aged men. *Int J Stroke* 2018; 13(3): 292–300.
22. Lauer MS, Levy D, Anderson KM, Plehn JF. Is there a relationship between exercise systolic blood pressure response and left ventricular mass? The Framingham Heart Study. *Ann Intern Med* 1992; 116: 203–210.
23. Lauer MS, Pashkow FJ, Harvey SA et al. Angiographic and prognostic implications of an exaggerated exercise systolic blood pressure response and rest systolic blood pressure in adults undergoing evaluation for suspected coronary artery disease. *J Am Coll Cardiol* 1995; 26: 1630–1636.
24. Mottram PM, Haluska B, Yuda S et al. Patients with a hypertensive response to exercise have impaired systolic function without diastolic dysfunction or left ventricular hypertrophy. *J Am Coll Cardiol* 2004; 43: 848–853.
25. Williams B, Mancia G, Spiering W et al. 2018 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). *Blood Press* 2018; 27: 314–340.



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## Section V

### Organ Damage-Measurement/Clinical Value

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# CARDIAC DAMAGE FROM LEFT VENTRICULAR HYPERTROPHY TO HEART FAILURE

# 29

Enrico Agabiti Rosei, Maria Lorenza Muiesan and Cesare Cuspidi

## INTRODUCTION

During the past 40 years, left ventricular hypertrophy (LVH), defined as an abnormal increase in the left ventricular mass (LVM), detected either by an electrocardiogram (ECG) or by the more sensitive echocardiographic technique, has been recognized as an important and independent risk factor in hypertension for predicting several cardiovascular events, including congestive heart failure (HF), sudden cardiac death, myocardial infarction and stroke.

## FROM LVH TO CHRONIC HF

From the earliest Framingham Heart Study report (1) on the prevalence of heart failure to the more recent demonstration of Vasan and Levy (2), hypertension remains one of the most common causes of cardiac failure; in the Framingham population the lifetime risk of heart failure at age 40 was 15.6 and 12% in normotensive men and women, respectively, and almost doubled (27.4 and 29.5%) in patients with BP > 160/100 (3). In the presence of a chronic pressure overload and neurohumoral stimulations, such as in arterial hypertension, various cellular responses are stimulated, including gene expression, protein synthesis, sarcomere assembly and cell metabolism, leading to the development of cardiac hypertrophy. In the development of hypertensive heart disease, myocyte hypertrophy is also associated with apoptosis and excess autophagy, inflammation, collagen deposition and ventricular fibrosis, with an impairment of coronary hemodynamics as well, thus profoundly influencing functional properties of the heart.

Hypertension is a risk factor of heart failure (HF) because it induces left ventricular (LV) cardiac structural and functional alterations, including the development of LVH, the impairment of LV relaxation and filling (so-called diastolic dysfunction) and the development of HF with preserved ejection fraction (HFpEF). In hypertension, the increased pressure load may also favour the development of coronary artery disease and LVH associated with enlargement of LV, with reduction of systolic function, as assessed by

ejection fraction, leading to HF with reduced ejection fraction (HFrEF).

Approximately half of the patients with overt chronic HF may display normal ejection fraction and marked impairment in diastolic function (3). Patients with heart failure with preserved ejection fraction (HFpEF) are usually older women with a long history of hypertension, frequently obese, with diabetes mellitus (DM), hyperlipidaemia and atrial fibrillation. Patients with HFpEF have a prevalence of hypertension up to 90% both in large randomized controlled trials and in epidemiological studies. They may have hypertensive pulmonary oedema as an expression of HFpEF.

The fundamental mechanisms contributing to the progression from compensatory LVH in hypertension to heart failure are still largely undefined (Figure 29.1) (4,5).

Cardiac hypertrophy involves a structural remodelling of cardiomyocytes and non-myocytes, and fibroblasts contribute to perivascular fibrosis that initially surrounds

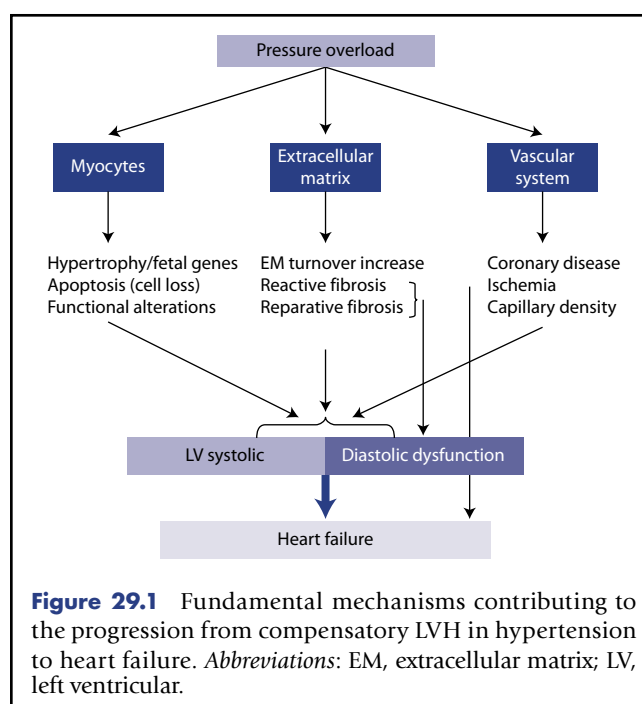


**Figure 29.1** Fundamental mechanisms contributing to the progression from compensatory LVH in hypertension to heart failure. Abbreviations: EM, extracellular matrix; LV, left ventricular.



intramural coronary arteries and thereafter moves into the interstitial space (6–8). The role of inflammatory cells and cytokines produced by the damaged myocardium in the development of interstitial fibrosis has been recently demonstrated (9), influencing the activity of the renin–angiotensin–aldosterone system (RAAS).

Collagen degradation is also impaired by the reduction of the activity of interstitial metalloproteinase-1 (MMP-1) activity and by the enhanced production of tissue inhibitor of metalloproteinases-1 (TIMP-1) in endothelial cells (8).

Several molecular mechanisms have recently been proposed to explain how hemodynamic and neurohumoral factors could induce the transition from hypertension to LVH and then to chronic HF. Although some of these mechanisms could become new targets for pharmacological interventions, their importance has not yet been completely established (5,8).

The postulated mechanisms that underlie cardiac dysfunction, alone or in combination, are hemodynamic load, decreased intrinsic myocardial contractility, adverse chamber remodelling, impaired coronary hemodynamics, and ventricular fibrosis.

The progressive increase in LV dimensions in patients with LVH is aimed to achieve a contractile reserve under conditions of stress. The adaptation of LV geometry to maintain cardiac output, however, increases wall stress that further influences cardiac dilatation, and this has been considered the first step in the transition from cardiac hypertrophy to cardiac failure (10). However, an interindividual variability in the magnitude of the increase in LV mass and change in geometry (ventricular dilation or wall thickening) has been observed and may be attributable to differences in the pressure load, concomitant medical conditions, neurohormonal activation or perhaps genetic influences (11).

## PATHOGENESIS OF CARDIAC STRUCTURE ADAPTATION

In arterial hypertension, elevated blood pressure is the fundamental trigger to the sequence of biological events that lead to development of LVH. Statistically, only 10% of the variation in LVM could be accounted for based on office systolic BPs averaged over a 30-year period (12). LVM is more closely related to average 24-h BPs (13,14), and even highly sophisticated measurements of BP cannot fully account for the variance in LVM (15). The circadian pattern of blood pressure appeared to be of further importance. Despite similar mean ambulatory blood pressure values, ‘non-dippers’ have increased LVM compared with individuals displaying the usual circadian pattern (14,16). Overall, 24-h mean BP and average daytime systolic BP – in most studies the best statistical correlates of LVM – account for about 25% of observed variance in LVM (17,18) and the simplistic view that only BP is a culprit of LVM has to be revised. It has been suggested that central SBP may be pathophysiologically more relevant than brachial SBP for the pathogenesis of cardiovascular disease (19). Central systolic BP has been associated more closely with LVH and carotid atherosclerosis as markers of hypertensive organ damage than brachial systolic BP in various populations (20–22).

Recently, it was observed that ambulatory central systolic BP, measured by 24-h BP monitoring, tends to be superior to brachial ambulatory systolic BP in predicting LVH (23).

Nonhemodynamic factors other than blood pressure, such as age, sex, race, body mass index, diabetes and dietary salt intake are operative in determining who among the hypertensive patients develop LVH and to what degree LVM is increased. Obesity is a major risk factor for LVH development: A 2 kg/m<sup>2</sup> increase in body mass index correlated with a 50% risk of increased LVM in a cohort of elderly men and women (24). Obese hypertensive patients are characterized by expanded plasma volume and increased cardiac output, both imposing an additional hemodynamic load on the left (and right) ventricle (25,26); in addition, the secretion of proinflammatory cytokines may contribute to adipocyte necrosis, and to the loss of vascular function contributing to LVH.

Epidemiological data clearly indicate that dietary salt intake modifies the process of LVH in hypertensive subjects as well (27,28). This has been reported irrespective of whether dietary salt intake has been assessed by measuring 24-h urine sodium excretion in clinical stable conditions or by directly measuring the salt ingested with food. Of note, this relationship has been found to be independent of 24-h blood pressure, body weight and other clinical determinants of LVH (28,29). In normotensive and hypertensive rats, high salt intake induced myocardial hypertrophy and fibrosis that was found to be related to increased aldosterone synthase activity and production of aldosterone in the myocardium despite decreased plasma renin activity and lowered plasma aldosterone concentration in the systemic circulation (30). Most recent trials have indicated that increases in intracellular sodium lead to an up-regulation of growth-stimulating genes, thereby directly inducing growth-stimulating signals.

Gender, race and genetic factors are also well established as nonhemodynamic factors that contribute to the development of LVH. In the Framingham Study, LVM increase was documented in a higher percentage of hypertensive women than men (70% compared with 31%), a difference which parallels the higher contribution of hypertension to the risk of chronic HF in women (31). In African Americans, the prevalence of LVH is greater as compared to whites at similar BP values (32). Several studies have further suggested that approximately 30% of the LVM variance is genetically determined (33). Studies of genetic influence of LVM have focused mainly on candidates’ genes that are related to the RAAS, to the sympathetic nervous system or its receptors, and on components of the signal transduction mechanisms involved in cardiac hypertrophy.

The effect of sympathetic nervous system is evident in experimental models and in human studies. Although in pheochromocytoma LVH prevalence is relatively low, new studies applying the cardiac spillover methodology and thereby assessing the direct effect of the sympathetic drive to the heart have found a close correlation between the cardiac noradrenaline spillover and LVM (34). These findings are in accordance with previous data demonstrating that increased peripheral muscle sympathetic nerve activity as measured by microneurography is elevated in hypertensive patients with LVH (34,35).

More recently, the role of beta-3 receptors (36) in protecting from cardiac fibrosis has been demonstrated; the stimulation of cardiac beta-3 receptors could influence nitric oxide and oxidant stress-dependent paracrine signalling to fibroblasts, reducing collagen synthesis.

Experimental and clinical trials highlight the role of the RAAS in mediating LVH (37,38). In particular,

inadequate suppression of the RAAS in relation to the dietary salt intake is related to an accelerated LVH (39). Angiotensin II acts primarily via the angiotensin type 1 receptor in myocytes, induces hypertrophy and hyperplasia, and regulates collagen synthesis. Angiotensin II production further upregulates expression of the fibrogenic cytokine TGF- $\beta$ 1, thereby inducing perivascular and interstitial fibrosis. The specific role of the angiotensin type 2 receptor is less clear, although its modulating effect on LVM has been pointed out by experimental and clinical data (40).

The coexistence of hypertension with diabetes increases the prevalence of LVH. Moreover, insulin resistance and high insulin levels are associated with the development of LVH in hypertensive patients (41). Other major metabolic cardiac risk factors, notably hypercholesterolemia and hyperglycaemia, may also modify the extent of LVM and the prevalence of LVH in the hypertensive population.

Both hemodynamic and nonhemodynamic factors are of pathogenetic importance for the development of LVH. Most evidence stems from experimental data, but several clinical trials clearly indicate that the variety of nonhemodynamic factors including dietary salt intake or neuroendocrine stimulation (sympathetic nervous system [SNS], RAAS) modify the adaptive response of the myocardium to increased cardiac workload in hypertension.

## EPIDEMIOLOGICAL AND CLINICAL ASPECTS OF CHRONIC HF IN HYPERTENSION

In about 70–75% of patients with chronic HF, an antecedent diagnosis of hypertension may be present. It has been also shown that LVH is a potent predictor of HF.

Most of the earlier randomised clinical trials evaluating the efficacy of antihypertensive drugs have demonstrated a significant change in hypertensive disease evolution. In fact, antihypertensive treatment may induce a significant prevention of systolic cardiac failure, thereby increasing patients' survival. Clinical manifestations of atherosclerotic disease, such as stroke and coronary artery disease, became more prominent causes of cardiovascular morbidity and mortality in hypertensive patients (41).

However, at the present time, with increased ageing of the general population, a persistent increase in morbidity and mortality associated with chronic HF has been observed (42,43). HF with preserved ejection fraction and diastolic dysfunction is more frequently observed in elderly hypertensive patients, in the presence of a reduced coronary flow reserve with or without associated epicardial coronary artery disease (43,44).

**Table 29.1** Proposed treatment for hypertension and hypertension and chronic heart failure/left ventricular hypertrophy, according to ESC/ESH guidelines 2018

### *Uncomplicated hypertension*

Among all antihypertensive drugs, ACE inhibitors, ARBs, beta-blockers, CCBs and diuretics (thiazides and thiazide-like drugs such as chlorthalidone and indapamide) are indicated as the basis of antihypertensive treatment strategies.

It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in an SPC. Exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is <150 mmHg).

Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise an RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic.

Beta-blockers are combined with any of the other major drug classes when there are specific clinical situations, e.g. angina, post-myocardial infarction, heart failure, or heart rate control.

If BP is not controlled with a two-drug combination, treatment should be increased to a three-drug combination, usually a RAS blocker with a CCB and a thiazide/thiazide-like diuretic, preferably as an SPC.

If BP is not controlled with a three-drug combination, treatment should be increased by the addition of spironolactone or, if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, a beta-blocker, or an alpha-blocker.

### *Hypertension and heart failure*

In hypertensive patients with heart failure (with rEF or pEF), BP-lowering treatment should be considered if BP is  $\geq 140/90$  mmHg.

In patients with HFpEF, BP treatment threshold and target values should be the same as for HFrEF.

In patients with HFrEF, BP-lowering treatment comprises an ACE inhibitor or ARB, and a beta-blocker and diuretic and/or MRA if required.

Dihydropyridine CCBs may be added if BP control is not achieved.

### *Hypertension and LVH*

Treatment with an RAS blocker in combination with a CCB or diuretic is recommended.

Systolic BP should be lowered to a range of 120–130 mmHg.

**Abbreviations:** ESC/ESH, European Society of Cardiology/European Society of Hypertension; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CCB calcium channel blocker; SPC, single pill combination; RAS, renin angiotensin system; MRA, mineral receptor antagonist.

Treatment of hypertension reduces the risk of HF, especially in elderly and very elderly patients, and prevention of HF represents the largest benefit associated with BP-lowering drugs (45) (Table 29.1). This has been observed using all five major classes of antihypertensive drugs, with diuretics being more effective, at least in preventing symptoms leading to HF hospitalization, and calcium channel blockers apparently less effective in comparative trials, although mainly in those trials in which they replaced diuretics. In the systolic blood pressure intervention trial (SPRINT) trial, patients submitted to an intensive treatment strategy had a significantly lower incidence of HF, although this may be related at least in part to the more intense use of diuretics (46).

## EVALUATION OF LVH

The presence of cardiac target-organ damage, and in particular of LVH, has prognostic relevance and may influence the choice of treatment options.

The recent guidelines of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) include echocardiography among the recommended techniques to be considered in hypertensive patients. Electrocardiography is widely available and specific but far less sensitive in detecting LVH (Tables 29.2 and 29.3) (45). Obesity may significantly impair the sensitivity of voltage-based criteria for LVH (47).

Echocardiography is a relatively easy method, is repeatable, is specific and is a more sensitive measure of LVH than electrocardiography. It is more expensive than electrocardiography but may provide additional information on the anatomy and function of the heart and valves and can be performed before starting antihypertensive therapy but also during treatment.

## CARDIAC STRUCTURE

In hypertensive patients, the main goal of echocardiography is the detection of LVH, and to this regard the calculation of LVM is mandatory. Hypertrophy cannot be defined according to wall thickness only, and wall thickness alone is not predictive of cardiovascular risk (48,49).

**Table 29.2** Electrocardiographic criteria for the definition of left ventricular hypertrophy derived from the ESC/ESH guidelines 2018

|                                      |                |
|--------------------------------------|----------------|
| SV1 + RV5 (Sokolow – Lyon criterion) | >35 mm         |
| R wave in aVL ≥                      | 11 mm          |
| SV3 + RaVL (Cornell voltage) a       | >28 mm (men)   |
|                                      | >20 mm (women) |
| Cornell duration product             | >2440 mm.ms    |

Note: Cornell voltage = Sum of limb and precordial lead voltage. Cornell product = Product of Cornell voltage × QRS duration (mm.ms).

Abbreviations: ESC/ESH, European Society Cardiology/European Society Hypertension.

**Table 29.3** Echocardiographic definitions of left ventricular hypertrophy, concentric geometry, left ventricular chamber size and left atrial dilatation derived from the ESC/ESH guidelines 2018

|                                                                                                              |
|--------------------------------------------------------------------------------------------------------------|
| <b>LVH</b>                                                                                                   |
| LV mass indexed to BSA, g/m <sup>2</sup> >95 in women, >115 in men (when BMI <30 kg/m <sup>2</sup> )         |
| LV mass indexed to height 2.7, g/m <sup>2.7</sup> >47 in women, >50 in men (when BMI >30 kg/m <sup>2</sup> ) |
| <b>Concentric geometry</b>                                                                                   |
| LV relative wall thickness (RWT) >0.43                                                                       |
| <b>LV dilatation</b>                                                                                         |
| Left ventricular end-diastolic diameter indexed to height, cm/m >3.3 in women, >3.4 in men                   |
| <b>Left atrial dilatation</b>                                                                                |
| Left atrial volume indexed to height <sup>2</sup> , mL/m <sup>2</sup> >18.5 in men and >16.5 in women        |
| Left atrial volume indexed to BSA >34 mL/m <sup>2</sup> (ASE/EAE)                                            |

Abbreviations: BSA, body surface area; BMI, body mass index; RWT, relative wall thickness; ESC/ESH, European Society of Cardiology/European Society of Hypertension; ASE, American Society of Echocardiography; EAE, European Association of Echocardiography.

Both mono-dimensional (M-mode) and two-dimensional (2D) echocardiography have been used in the measurement of LVM and have been anatomically validated (50,51).

Linear measurements of interventricular septal wall thickness (IVST), as well as of left ventricular internal diameter (LVID) and posterior wall thickness (PWT), should be obtained with the beam perpendicular to the minor axis at the mitral valve leaflet tips, in the left parasternal acoustic window, at end diastole, from 2D-targeted M-mode or directly from 2D images. Calculation of LVM is based on a mathematical formula assuming a prolate ellipsoid shape for the LV ( $LVM = 0.8 \times (1.04[(LVIDD + PWTD + IVSTD)^3 - (LVIDD)^3]) + 0.6$  g, where LVIDD is left ventricle internal dimension in diastole, PWT is posterior wall thickness in diastole and IVSTD is intraventricular septal thickness in diastole (52).

LVM normalization for an anthropometric measure, such as height or body surface area, is needed to identify LVH. Weight and height should be measured simultaneously to the echocardiographic examination, avoiding the use of patient's self-reported data, which is a source of potential error in the indexation of LVM, and finally in the risk stratification (53). The indexation of LVM to body surface area underestimates the prevalence of LVH and the LVH-attributable risk in populations with overweight or obese subjects (53). In these patients, indexation of LVM for height (height to the allometric power of 1.7 or 2.7) can be considered. Indexation by height 2.7 was derived from a cohort of Caucasian children and adults and indexation by height 1.7 was derived from a study including 1035 Chinese and Caucasian adults (54,55). Recent data from the EchoNoRMAL (Echocardiographic Normal Ranges Meta-Analysis of the Left Heart) suggest that different allometric power for body surface area

(BSA) and height should be applied according to gender and ethnic group (56).

The evaluation of geometric adaptation of the left ventricle to the increased hemodynamic load implies the calculation of the relative wall thickness (or wall-to-radius [WTR] ratio, i.e. the ratio between LV end-diastolic wall thicknesses and diameter) and may significantly differ among hypertensive patients (57). A cutoff value of 0.43 permits categorization of an increase in left ventricular mass as either concentric ( $RWT \geq 0.43$ ) or eccentric ( $RWT < 0.43$ ) hypertrophy, and also allows the identification of concentric remodelling, defined as a normal LVM with increased  $RWT \geq 0.43$  (45).

These different LV geometric patterns are associated with different hemodynamic characteristics, and peripheral resistances are greater in patients with concentric geometry while cardiac index is increased in those with eccentric hypertrophy (58). In addition, concentric remodelling and eccentric and concentric hypertrophy all predict an increased incidence of cardiovascular disease, but concentric hypertrophy has consistently been shown to be the condition that most markedly increases the risk, even in very-high-risk patients (59–61). Recently, a new reclassification of LVH, based on LVM, RWT and LV dilatation has been proposed in hypertensive patients (62). Eccentric LVH with increased LV chamber volume predicted increased risk for all-cause and cardiovascular mortality and cardiovascular events, while eccentric hypertrophy with normal LV chamber size did not. In contrast, both dilated and nondilated concentric LVH are associated with poor outcome. The low-risk group of patients with relatively mild eccentric LVH, no concentric geometry or dilatation had a similar risk of all-cause mortality or cardiovascular events as patients with normal LVM. Verification of the enhanced prognostic power of the four-group classification of LVH in other populations is needed before recommending that this more refined approach replace the established classification of LVH into eccentric and concentric subgroups.

Evaluating LVM increase by taking into account gender and cardiac loading conditions has been proposed in order to discriminate the amount of LVM adequate to compensate the hemodynamic load (adequate or appropriate) from the amount in excess to loading conditions (and therefore inappropriate or not compensatory) (63). LVM is inappropriate when the value of LVM measured in a single subject exceeds the amount needed to adapt to the stroke work for that given gender and body size. The degree of LV mass inappropriateness is associated with structural and functional abnormalities, such as concentric LV geometry, reduced LV ejection fraction and midwall shortening, and prolonged LV relaxation, and with an increased rate of cardiovascular events, both at baseline and during treatment (64). In the Cardiovascular Health Study population, the hazard of heart failure increased by 1% for each 1% increase in inappropriate LV mass and by 3% for each  $g/m^{2.7}$  increase in traditionally measured LV mass index, confirming that the excess of LV mass portends impending heart failure (65).

Technical variability represents a potential limitation of echocardiographic measurement of LVM. An assessment of LVM reproducibility has shown that LVM changes of 10–15% may have biological significance in individual patients (66). When changes in LVM inappropriateness are evaluated, changes of 15–25% may reflect true change (67). Despite the fact that the relationship between LVM and incidence of cardiovascular events is continuous (68), several

criteria for the diagnosis of echocardiographic LVH have been proposed. These criteria are based on the distribution of LVM index in general population samples (average LVM value plus one standard deviation in apparently healthy population-based samples) or on the association between increased values of LVM and occurrence of cardiovascular events in longitudinal studies. The presence of echocardiographic LVH is associated with an incidence of cardiovascular events equal to or greater than 20% in 10 years (69).

The American Society of Echocardiography and the European Association of Echocardiography (ASE/EAE) have published ranges for several echocardiographic parameters derived from a population of about 500 multi-ethnic, normotensive and normal weight subjects, and the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study has provided new reference limits in an Italian population (70). A revision of previous diagnostic criteria will probably come from new ethnic- and gender-specific group reference values from the EchoNoRMAL project (56). Real-time 3D echocardiography permits a more reliable measurement of LVM, and its accuracy has been shown to compare favourably with that of cardiac magnetic resonance imaging (71).

Similar to magnetic resonance imaging (MRI), not currently recommended for the assessment of hypertensive heart disease in clinical practice, 3D echocardiography has the advantage of not relying on geometric formulas for calculating LVM but of measuring it directly. This allows greater accuracy and reproducibility in the evaluation of the LV structure and geometry in comparison with standard echocardiography. Numerous studies carried out in healthy subjects from different ethnic groups have investigated the accuracy of 3D echocardiography for LVM measurements against MRI and have found an excellent correlation between the two methods (72). However, criteria for prognostic significance of increased LV mass by 3D echocardiography are not yet clearly established.

## ASSESSMENT OF LV DIASTOLIC FUNCTION

A large number of patients with typical symptoms of chronic HF present a normal or only mildly impaired systolic function but have evidence of diastolic dysfunction (73–77). In hypertensive patients, diastolic dysfunction is characterized by alterations of LV relaxation and filling, which may precede abnormalities of systolic function; these abnormalities should be interpreted according to the presence of LVH or concentric geometry in order to give a correct interpretation of LV diastolic function and filling pressure parameters. In fact, in patients with LVH or concentric remodelling, LV relaxation is usually slowed, with a decrease in early diastolic filling; in the presence of normal left atrial pressure, a greater proportion of LV filling is shifted from early to late diastole after atrial contraction. Therefore, the presence of a predominant early filling in these patients should suggest the presence of increased LV filling pressures (78).

These aspects have become even more relevant owing to the increase of the elderly population in Western countries. Diastolic dysfunction can be observed in a greater percentage of patients with LVH. Increasing age, higher heart rate and obesity may worsen diastolic filling. Gender-related differences have been observed in the impact of impaired diastolic relaxation on exercise capacity in hypertensives with LVH, and females could be more likely to have an altered cardiac adaptation to physical activity than males.



Recent reports identify elderly women as the most likely candidates for the development of HFpEF.

HFpEF may be observed in approximately 50% of all heart failure cases, and it may be associated with similar mortality and morbidity rate compared to heart failure with reduced EF. It is conceivable that early recognition and appropriate therapy of diastolic dysfunction can prevent further progression to HFpEF and death (79).

Myocardial relaxation reflects the time course and extent of cross-bridge dissociation after systolic contraction. The load imposed on the muscle, the rapid reduction of cytosolic calcium to baseline levels and alterations in sensitivity of myofilaments to calcium may profoundly modify myocardial relaxation. Myocardial relaxation alterations may be related to the down-regulation and reductions in protein levels of sarcoplasmic reticulum pumps ATP-dependent, influencing the time course of calcium transient and the frequency-force response. In addition, the increase of beta-myosin ATP-ase activity and the changes in troponin subunit isoform expression and phosphorylation represent other molecular adaptations affecting myocardial relaxation. The increase of isovolumic relaxation time due to a slower and delayed relaxation is frequently observed in hypertensive patients. Invasive techniques with cardiac catheterization and simultaneous pressure and volume measurements represent the gold standard to assess left ventricular diastolic function, with measurement of the rate of left ventricular relaxation, and the rate and timing of diastolic filling as well as myocardial stiffness; however, these techniques are clearly unpractical for routine diagnostic evaluation, which is relevant in the large population of hypertensive patients (80).

Passive filling dynamics are influenced also by alterations of passive deformation properties of the myocardium, interestingly not only related to the wall thickness but also, most importantly, to its composition, i.e. mainly interstitial and perivascular fibrosis. The increase in extracellular matrix collagen tissue may be promoted by the stimulation of the RAAS. Several studies evaluating serum levels of matrix metalloproteinases (associated with increased collagen accumulation) and tissue inhibitor of matrix metalloproteinases showed the progressive changes in the extracellular matrix with transition from LVH to symptomatic heart failure with a preserved EF (81) (Table 29.4).

Subendocardial ischemia, typically seen in patients with LVH even in the presence of normal epicardial arteries, can deteriorate diastolic filling. Conversely, since most of the coronary flow occurs in diastole, alterations of myocardial relaxation or compliance may affect blood supply. Diastolic abnormalities may be observed early in the natural history of hypertension and may also be demonstrated in normotensive subjects with parental hypertension (82,83). A few studies, using different techniques, showed that diastolic LV performance significantly influences exercise capacity in hypertensive patients with LVH (84–87). Brogan et al. (75) and Fagard et al. (88), who defined diastolic dysfunction on the basis of left ventricular end diastolic pressure or pulmonary wedge pressure, respectively, found an association between diastolic dysfunction and subsequent incidence of heart failure or cardiovascular events.

An improvement in the study of LV diastolic function has been provided by the assessment of Doppler transmitral flow velocities and by pulsed Doppler tissue imaging (DTI). Left atrial (LA) size is a further parameter to be assessed in the evaluation of diastolic function (89).

**Table 29.4** Structural, functional and ultrastructural LV characteristics in HFpEF and HFrEF

|                              | HFpEF                 | HFrEF             |
|------------------------------|-----------------------|-------------------|
| <i>LV structure/function</i> |                       |                   |
| End-diastolic volume         | ↔                     | ↑                 |
| End-systolic volume          | ↔                     | ↑                 |
| Wall thickness               | ↑                     | ↔                 |
| Mass                         | ↑                     | ↑                 |
| Mass/volume ratio            | ↑                     | ↓                 |
| Remodelling                  | Concentric            | Eccentric         |
| Ejection fraction            | ↔                     | ↓                 |
| Stroke work                  | ↔                     | ↓                 |
| End-systolic elastance       | ↔                     | ↓                 |
| End-diastolic stiffness      | ↑                     | ↓                 |
| <i>LV ultrastructure</i>     |                       |                   |
| Myocyte diameter             | ↑                     | ↔                 |
| Myocyte length               | ↔                     | ↑                 |
| Myocyte remodelling          | Concentric            | Eccentric         |
| Fibrosis                     | Interstitial/reactive | Focal/replacement |

The influence of factors such as age, gender, body mass index, heart rate and blood pressure on Doppler flow velocities has been extensively evaluated. Normal values for Doppler parameters according to age groups have been assessed in a relatively small sample of 117 subjects (90).

The analysis of myocardial velocities at the mitral annulus may reveal an increase in left ventricular filling pressure; in respect to Doppler transmitral flow velocities, DTI velocities show no 'pseudonormalisation' pattern (91,92). The average value of DTI velocities at the septal and lateral sides of the mitral annulus should be used for the assessment of global LV diastolic function. The E/e' ratio represents a reliable estimate of LV filling pressures, and different cutoff values have been proposed for the definition of normal or progressively higher LV filling pressure. E/e' ratio >13 indicates a severe increase in LV filling pressure. In the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) echocardiographic sub-study, E/e' ratio was the strongest predictor of first cardiac events, independent of LVM and geometry (93). The combination of transmitral flow velocities, mitral annulus DTI velocities and LA volume should be used for diastolic dysfunction diagnosis and stratification (92). The grading suggested by the EAE/ASE recommendations is an important predictor of all-cause mortality, as shown in the Olmsted County Epidemiological Study (Figure 29.2).

An accurate measurement of LA size should be an integral part of the standard echocardiogram in hypertensive patients. LA enlargement may reflect the increase in LV filling pressure; in patients with preserved systolic function it may be a marker of diastolic dysfunction and is predictive



| Type of trial                     | Trials | HF events(n/pts) |                 | Difference SBP/DBP | Standardized RR (95%CI) |
|-----------------------------------|--------|------------------|-----------------|--------------------|-------------------------|
| <i>Trials with no baseline HF</i> |        | <i>Treated</i>   | <i>Controls</i> |                    |                         |
| Intentional                       | 13     | 260/17103        | 379/15830       | −9.4/−4.8          | 0.58 (0.45–0.72)        |
| Intentional + Non-intentional     | 18     | 997/30519        | 1276/29331      | −6.7/−3.4          | 0.58 (0.44–0.75)        |
| <i>Trials with no or mild HF</i>  |        |                  |                 |                    |                         |
| Intentional                       | 19     | 574/31691        | 787/30118       | −8.5/−3.9          | 0.55 (0.41–0.71)        |
| Intentional + Non-intentional     | 28     | 1688/55324       | 2027/53279      | −6.2/−3.0          | 0.58 (0.47–0.72)        |

**Figure 29.2** Relative risk reduction of heart failure (HF) in blood pressure-lowering in trials with no baseline heart failure and with no or mild baseline heart failure. (From Thomopoulos C et al. *J Hypertens.* 2016 March;34(3):373–384.)

of an increased risk of atrial fibrillation, stroke, heart failure and mortality. This has been shown by the measurement of LA anteroposterior linear dimension by M-mode from the parasternal long axis view and by the more accurate evaluation of LA volume from 2D images. The measurement of LA volume is recommended both in clinical practice and in research studies, and most guidelines recommend the biplane area-length method. The 2013 ESH/ESC hypertension guidelines and the EAE/ASE guidelines recommend a cutoff value of  $>34 \text{ mL/m}^2$  for left atrial enlargement (94), while the 2018 ESH/ESC guidelines have further suggested the indexation of LA volume to height<sup>2</sup> for the evaluation of LA enlargement (45).

Compared to the conventional 2D approach, 3D echocardiography appears superior in the assessment of LA volume; at present, however, this application is limited to research studies. The same consideration applies to several other parameters of LA function, based on 2D or 3D measures, conventional and tissue Doppler or strain rate imaging (95,96).

LA reservoir and conduit function, assessed by volumetric and strain analysis, have been shown to be significantly impaired in hypertensive patients when compared to normotensive controls.

Some authors have found that all LA functions are reduced in hypertensive patients, while other investigators reported decreased conduit and enhanced LA reservoir and pump function (97). In addition, other researchers have demonstrated reduced LA reservoir and conduit, but compensatory increased booster pump LA function.

## ASSESSMENT OF LV SYSTOLIC FUNCTION

LV dysfunction includes segmental and global alterations of LV that may differently affect pump function and prognosis. In uncomplicated hypertensive patients LV fractional shortening (FS) and ejection fraction (EF) express endocardial fibre shortening and are usually preserved or even 'supernormal', mainly in the presence of concentric geometry. However, midwall myocardial fibres contribute to a greater extent than subendocardial fibres to LV ejection, and the difference between the conventional and midwall indexes of LV systolic function is more evident in the presence of a concentric LV geometry; therefore, in

the presence of a concentric LV geometry, LV midwall FS is considered a more appropriate index of LV systolic function than conventional FS (98–100). The regression of LVH in patients with reduced midwall systolic performance is associated with a significant improvement of FS (101–103).

Left ventricular ejection fraction (LVEF), derived from 2D calculation of the LV end-diastolic volume (EDV) and the LV end-systolic volume (ESV) according to the modified Simpson method (average of apical four- and two-chamber views) is the most sensitive index of systolic ventricular function, with a high prognostic value. LVEF values  $>55\%$  define a normal systolic function, while a slight or moderate reduction in systolic function is present when EF values are between 45–55% and between 35–45%, respectively; values below 35% identify patients with severe LV systolic dysfunction.

In the absence of major structural abnormalities, a single-plane measurement of the LV area is obtained from the apical four-chamber window. The longitudinal myocardial systolic velocity (Sm), measured by tissue Doppler imaging (TDI) at the mitral annulus level, has been proposed as a reliable and accurate index of myocardial fibre performance, independent of LV preload and afterload. In normal conditions its value is higher than 8 cm/s and in severe pathological conditions is less than 5 cm/s.

More recently, a 3D probe (multiplane) has become available and allows the calculation of LV volumes by the Simpson triplane method (104). The accuracy of 3D echocardiographic examination in the measurement of LV volumes has been confirmed by comparison with MRI (105).

The newly developed 2D and 3D speckle tracking echocardiography (a technique based on the analysis of interference patterns and natural acoustic reflections generated by tissue motion which are ultimately resolved into angle-independent 2D and 3D strain-based sequences) represents a valuable tool for the detection of subclinical systolic dysfunction in the hypertensive setting and allows estimation of different directional strain components (106,107).

Left ventricular motion is rather complex and involves different types of movements: shortening, thickening, lengthening, rotation, twist and untwist. The best echocardiographic method for evaluation of these complicated cardiac motions is speckle-tracking imaging (STI). Strain is only one of the STI parameters and represents a percentage in changes of myocardial longitudinal

diameter (longitudinal strain), circumference (circumferential strain) and thickness (radial strain) (108). Apical rotation in the clockwise direction and basal rotation in the counterclockwise direction enable efficient cardiac contraction. Twist is the mathematical summation of the absolute values of the basal and apical rotations. This complex cardiac motion may be explained by cardiac layer architecture (109). LV myocardial wall consists of three layers: endocardium, mid-myocardium and epicardium. Subendocardial and subepicardial myocytes have mostly longitudinal direction, whereas mid-myocardial myocytes are circumferentially directed. The assessment of global LV strain, and especially longitudinal strain, has been widely accepted in the clinical practice, because it is an angle-independent, significantly less load- and age-dependent than TDI, reproducible tool with high predictive value in patients with a wide range of cardiovascular diseases including arterial hypertension. STI strain rates are parameters derived from global strain and illustrate systolic, early and late diastolic LV function, similar to TDI indexes.

Of all available strain parameters, LV global longitudinal strain certainly has the most importance and the greatest clinical utility. Recent studies showed that LV global longitudinal strain represents a good predictor of cardiovascular and total morbidity and mortality in the hypertensive population or in the large group of patients with high prevalence of different cardiovascular risk factors, of which arterial hypertension was present in more than 40% (110). Arterial hypertension has an impact on all myocardial layers. Kim et al. (111) showed that all endocardial, midcardial and epicardial longitudinal strains were lower in hypertensive patients than in controls. Other authors showed that mostly endocardial and mid-myocardial layers are impaired in different hypertensive settings (i.e. white-coat, masked and sustained hypertension). The available evidence regarding LV circumferential strain in the hypertensive population is not consistent. Some authors found significantly lower values of LV circumferential strain, while others disagreed. Most of the circumferential changes found in hypertensive patients were ascribed to LVH. However, our findings in prehypertensive and white-coat hypertensive patients showed that LVH is not crucial for deterioration of circumferential strain. On the other hand, researches have also suggested that LV geometry, and particularly concentric and concentric-dilated LVH patterns, are responsible for worsening of LV circumferential strain (112).

## CONSEQUENCES OF LVH AND HF

### LVH AND ISCHEMIA

LVH and failure are frequently associated to coronary artery disease. Hypertension is one of the major risk factors for coronary atherosclerosis.

In the assessment of LVH by electrocardiographic criteria, the use of the pattern of 'definite LVH', including S-T segment and T wave abnormalities, was strongly associated with an increase of the incidence in acute myocardial infarction and sudden death (1,113,114). When using the voltage criteria for LVH, a less strong association with myocardial infarction was observed, suggesting that

alterations in the repolarization could reflect the presence of reduced coronary perfusion.

It has been shown that the presence of LVH is associated with structural and functional alterations in both large (115–117) and small arteries (118–121). Vascular structural changes are particularly evident in patients with concentric remodelling and LVH (122–124).

The presence of vascular alterations is in large part responsible for reduced coronary reserve, consistently observed in patients with LVH (125).

The concomitant atherosclerotic process of epicardial coronary vessels (126) and the structural alterations (127) and rarefaction of small coronary vessels limit blood supply in a situation where oxygen request is increased due to the greater mass of tissue. An insufficient compensatory angiogenesis has been also demonstrated during the development of adult LVH (128).

Wall motion abnormalities during a stress test have a high specificity for epicardial coronary artery stenosis assessed by angiography. In hypertensive patients with LVH and/or microvascular disease, myocardial perfusion abnormalities are frequently observed despite normal coronary arteries at angiography (129). The use of echocardiographic imaging of wall motion abnormalities and of coronary flow reserve in the left anterior descending artery in order to distinguish the presence of obstructive coronary artery disease (wall motion alterations and reduced coronary flow reserve) from microvascular disease (reduced coronary flow reserve and normal regional wall motion) has been proposed (130).

In the presence of LVH, the decrease of coronary perfusion in subendocardial layers may yield to myocyte necrosis and reparative fibrosis (131), favouring the progression to heart failure.

Other extravascular mechanisms potentially responsible for impaired coronary reserve include changes in wall tension, heart rate and contractility. In fact, oxygen requirements, as measured by the triple product (heart rate  $\times$  LV mass  $\times$  end-systolic stress) are progressively increased in patients with LVH in comparison to patients with normal LV mass and geometry (132).

The reduction of the regulatory capacity of coronary flow is greater during exercise, when oxygen demand increases. In fact, in resting conditions the reduction in coronary flow reserve may not have important consequences, but during exercise-induced increase in oxygen requirement it may become clinically relevant, producing the clinical manifestations and favouring the progression of LV dysfunction (133).

Functional alterations may occur and further deteriorate the vasodilator response of coronary microcirculation. Functional alterations related to endothelial dysfunction have been shown to precede morphological changes in the vascular wall and may trigger the development of vascular remodelling (134,135) (Table 29.5).

All these observations suggest that LVH represents a state of potential or actual myocardial ischemia.

### LVH AND VENTRICULAR TACHYARRHYTHMIAS

The clinical spectrum of hypertensive heart disease ranges from impaired coronary reserve, impaired filling, impaired pumping function and ventricular remodelling to cardiac arrhythmias such as ventricular ectopy and

**Table 29.5** Mechanisms for coronary flow reserve reduction in the presence of LVH

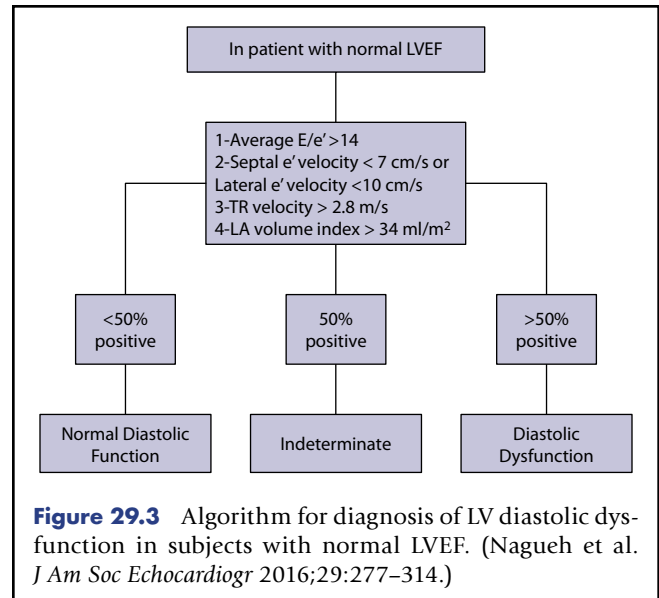
|                                                                                 |
|---------------------------------------------------------------------------------|
| <i>Myocardium</i>                                                               |
| Myocyte hypertrophy                                                             |
| Perivascular and interstitial fibrosis                                          |
| Extravascular compression (wall stress increase and abnormal diastolic filling) |
| Oxygen requirement increase                                                     |
| <i>Coronary vasculature</i>                                                     |
| Atherosclerosis of coronary epicardial vessels                                  |
| Structural alterations of small vessels (media thickening)                      |
| Arteriolar rarefaction (or insufficient compensatory angiogenesis)              |
| Endothelial dysfunction                                                         |

Abbreviation: LVH, left ventricular hypertrophy.

atrial fibrillation. As early as 1984, Messerli reported that hypertensive patients with LVH have a significantly greater prevalence of premature ventricular contractions and complex ventricular arrhythmias than patients without LVH or normotensive subjects (136); this finding was later confirmed in large population-based studies (137,138). Hence, the presence of ECG criteria of LVH represents a risk of higher incidence of sudden death that is most prominent in women (139).

On the basis of epidemiological observations, a pathophysiological chain of evidence linking hypertension, LVH and sudden death has been proposed (137–141). Furthermore, the Framingham cohort indicated that in patients with LVH the presence of symptomatic ventricular arrhythmias was associated with a nearly twofold increase in mortality (137). Hypertensive patients with LVH also have more ventricular arrhythmias during the interval from 6:00 AM to noon, an interval when cardiac death is most frequent (142). This observation and the evidence of increased ventricular vulnerability detected by different techniques (late potentials, ST depression on Holter recording, programmed ventricular stimulation, changes in the fibrillation threshold) support the link between ventricular ectopy and cardiac sudden death in hypertensive patients (138).

However, the mechanism by which LVH leads to increased arrhythmogenicity and ultimately to increased mortality still remains to be elucidated. In a follow-up trial of a geriatric population, hypertensive patients without documented coronary artery disease but with echocardiographic LVH were more likely to experience ventricular fibrillation or sudden death than their counterparts without LVH (31% vs. 10%) (143). Potential mechanisms are subendocardial ischemia, cardiac hypertrophy, high blood pressure by itself, irregular hypertrophic pattern, fibrosis within the myocardium (interstitial as well as perivascular) and the hypertrophic cardiac myocyte per se (Figure 29.3). Furthermore, excessive activity of the sympathetic nervous system and the RAAS exert indirect or direct arrhythmogenic effects (141).



Since numerous studies have documented that LVH per se is associated with ventricular arrhythmias (139), one would expect that these ventricular arrhythmias would disappear with reduction of LVH. In a double-blind study, the use of ACE inhibitors led to a significant reduction in LVH, and at the same time, to a marked reduction in ventricular ectopy, whereas in the placebo group LVH progressed and no changes in ventricular ectopy occurred (144). In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, the absence of in-treatment ECG LVH in hypertensive patients with baseline ECG LVH was associated with a reduced risk of sudden cardiac death independent of antihypertensive treatment regimen, blood pressure reduction, prevalent coronary heart disease, and other cardiovascular risk factors (145). Overall, reduction in ventricular ectopy has been found with the use of calcium antagonists, ACE inhibitors, angiotensin II receptor blockers and beta-blockers (143–145) (Table 29.6). The fact that ventricular ectopy disappeared with three different drug classes makes it unlikely that the underlying mechanism is a direct antiarrhythmic effect of any drug on the ectopically firing myocardium. The potential proarrhythmogenic effect of diuretics is matter of concern, since diuretics have been shown to increase ventricular ectopy both at rest and during exercise (146). This

**Table 29.6** Proposed treatment of hypertension and coronary artery disease according to ESC/ESH guidelines 2018

Target SBP to  $\leq 130$  mmHg if tolerated, but not  $< 120$  mmHg

In older patients (aged  $\leq 65$  years), target to an SBP range of 130–140 mmHg

Target DBP to  $< 80$  mmHg, but not  $< 70$  mmHg

In hypertensive patients with a history of myocardial infarction, beta-blockers and RAS blockers are recommended as part of treatment

In patients with symptomatic angina, beta-blockers and/or CCBs are recommended

proarrhythmogenic effect may result from intracellular electrolyte shift. Whether the reduced ventricular ectopy transfers into improved cardiovascular prognosis and less cardiac sudden death remains to be documented.

## LVH AND ATRIAL FIBRILLATION

Data from the Framingham Study also support evidence of an increased prevalence of atrial fibrillation among patients with hypertensive cardiovascular disease as compared with control subjects both in men (risk ratio 2.1) and women (risk ratio 1.9) (147,148). Among different cardiovascular risk factors, LVH was found to be a better predictor of atrial fibrillation than smoking, hypertension or diabetes (148). Subsequent studies showed that both left atrial chamber diameter and LVM independently predicted the development of atrial fibrillation, besides age. Hypertensive heart disease is therefore the most prevalent and potentially modifiable independent risk factor for the development of atrial fibrillation and its complications, including thromboembolism.

As a consequence, blood pressure control may be the common opportune strategy for the prevention of atrial fibrillation (149–151). If LVH coexists, treatment should aim at not only controlling blood pressure but also reducing LVH. In hypertensive patients with LVH diagnosed by ECG (LIFE study) angiotensin receptor blocker (ARB) (losartan)–based therapy was more effective than beta-blocker–based (atenolol) therapy in reducing the incidence of new-onset atrial fibrillation and the associated cardiovascular morbidity and mortality (149). New onset of atrial fibrillation occurred in 150 patients randomized to losartan versus 221 to atenolol (6.8 vs. 10.1 per 1000 person-years: relative risk 0.67) despite similar blood pressure reduction (149). In accordance with the LIFE trial, in hypertensive patients with high cardiovascular risk ARB (valsartan)–based treatment prevented new onset of atrial fibrillation to a greater extent than calcium antagonist (amlodipine)–based treatment. Throughout the follow-up period, atrial fibrillation was newly observed in 252/6278 hypertensive patients on valsartan as opposed to 299/6888 hypertensive patients on amlodipine. The corresponding hazard ratio for at least one occurrence of atrial fibrillation was 0.84 ( $p < 0.045$ ) and of persistent atrial fibrillation 0.68 ( $p < 0.005$ ) in the VALUE trial, which remained significant even after adjusting for LVH at baseline, age and history of coronary heart disease (151) (Table 29.7).

Treatment with ACE inhibitors does not have strong evidence that the incidence of new onset atrial fibrillation in hypertensive patients may be reduced; in the only two available prospective trials with ACE inhibitors no such effect was observed (152,153), whereas according to a retrospective longitudinal cohort analysis from a database of 8 million patients in a managed care setting ACE inhibitors were associated with a lower incidence of atrial fibrillation in comparison with calcium antagonists (154). Also, the combination of amiodarone with ARB or ACE inhibitor is able to maintain sinus rhythm more efficiently than amiodarone therapy alone (155,156).

Some other data come from more recent trials. In the ONTARGET trial (157), new atrial fibrillation was just slightly less frequent with the ARB (telmisartan) than

**Table 29.7** Pathophysiological and clinical consequences of LVH and LVH regression

|                                                | Presence of LVH             | Reversal of LVH                            |
|------------------------------------------------|-----------------------------|--------------------------------------------|
| Systolic dysfunction                           | Depressed midwall FS or GLS | Unchanged (or improved midwall FS and GLS) |
| Diastolic filling and relaxation abnormalities | Present                     | Unchanged or improved                      |
| Autonomic nervous system function              | Present                     | Changes toward normalization               |
| Ventricular arrhythmias                        | Frequently present          | Reduced number                             |
| Atrial fibrillation                            | Frequently present          | Reduced incidence                          |
| Coronary reserve                               | Reduced                     | Improved                                   |
| Associated vascular structural changes         | Present                     | Improved                                   |

Abbreviations: LVH, left ventricular hypertrophy; FS, fractional shortening; GLS, global longitudinal strain.

with the ACE inhibitor (ramipril) treatment, indicating no difference between these two types of renin–angiotensin system (RAS) blockade. The placebo comparisons in the TRANSCEND (158) and the PROFESS (159) trials could not confirm a protective effect of ARBs against onset of atrial fibrillation, although the absolute numbers were low, and the detection power of the analysis may have been insufficient.

In the largest trials with hypertensive patients (LIFE trial, VALUE trial) the difference in favour of the ARBs remained significant even after adjusting for in-treatment blood pressure and LVH (148,151). This points to the fact that in addition to blood pressure control and effective reduction of LVH, other factors might be of pathogenetic importance. Indeed, RAS blockade has been found to prevent left atrial dilatation and atrial fibrosis, to slow conduction velocity and to exert direct anti-arrhythmogenic effects (152,159). Beyond that, there is increasing evidence that inflammation in the left atrium is of pathogenetic relevance for the development of atrial fibrillation, and consequently drugs with anti-inflammatory potential such as ARBs or statins facilitate the prevention of atrial fibrillation (159,160).

In a meta-analysis by Schneider et al. (161), RAS blockade reduced the odds ratio for atrial fibrillation by 32% (0.22–0.43,  $P < 0.00001$ ), with similar effects of ACEIs and ARBs. In primary prevention, RAS blockade was most effective in patients with LVH and/or heart failure. In secondary prevention, RAS blockade reduced the odds for atrial fibrillation recurrence after cardioversion by 45% (0.34–0.89,  $P < 0.01$ ) and on medical therapy by 63% (0.27–0.49,  $P < 0.00001$ ).

Two larger studies (Candesartan in the Prevention of Relapsing Atrial Fibrillation [CAPRAF] and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca atrial fibrillation [GISSI-AF]) failed to demonstrate any benefit of therapy with either candesartan or valsartan for preservation of sinus rhythm after cardioversion.



In conclusion, drugs blocking the RAAS may reduce the risk of new-onset atrial fibrillation. Nevertheless, this effect has been mainly observed in high-risk patients particularly in those with left ventricular dysfunction or LVH and in post-myocardial infarction patients. Most of the supportive data come from post hoc analyses (162).

### CLINICAL CONSEQUENCES OF CHANGES OF LV MASS DURING ANTIHYPERTENSIVE TREATMENT

Antihypertensive treatment is associated with a significant reduction in LVM. The magnitude of the decrease is related to the baseline LVM (163); according to variability in LVM measurements only changes >10–15% can be considered of biological relevance (66). The correlation between changes of LVM and changes in clinic BP is modest and is improved when 24-hour BP is considered (17).

Among all classes of antihypertensive drugs, ACE inhibitors, ARBs and calcium antagonists seem to be more effective as compared with beta-blockers (164). It should be kept in mind, however, that in most studies patients were receiving a combination of drugs (usually with a diuretic) and not monotherapy. In addition, the recent ESH/ESC European guidelines (45) indicate initiation of antihypertensive treatment in most patients with a combination of drugs, i.e. a RAS blocker plus a calcium-antagonist and/or a diuretic. The efficacy of antihypertensive treatment in inducing adequate and long-term blood pressure control seems more important than the choice of a specific class.

A normalization of LVM is more difficult and cannot be always reached in women, obese or diabetic patients (165), elderly subjects with isolated systolic hypertension (166) or patients with coronary artery disease, despite adequate treatment. A normalization of LV geometry is also possible and in the LIFE study a conversion of concentric to eccentric LVH was reported in 34% of subjects, whereas only 3% of patients with eccentric LVH transitioned to concentric LVH (167). In the ASCOT study a modest change in LVM and persistence of elevated relative wall thickness were observed from the first to the third year of therapy (168).

Several studies have also noted an improvement of midwall FS (102) and of diastolic function parameters in response to antihypertensive therapy. However, two studies have recently shown no favourable changes in diastolic filling or E/e' ratio ratio, despite adequate BP control (168,169); in these studies, however, a limited, albeit statistically significant, decrease of LVM and no change in RWT were noted.

It is possible that the partial dissociation between structural and functional changes during antihypertensive treatment may reflect, at least in part, the effect of treatment on several factors influencing diastolic function, including heart rate, humoral changes and extracellular matrix composition.

The deposition of perivascular and interstitial fibrosis has been noninvasively evaluated by some ultrasound methods, showing that drugs interfering with the RAAS may be particularly effective in inducing changes that might reflect a decrease of myocardial tissue collagen content. Cardiac magnetic resonance may provide accurate and noninvasive assessment of regional myocardial fibrosis using late gadolinium enhancement, while

diffuse interstitial myocardial fibrosis is accurately assessed with post-contrast T1 mapping. In the future this technique will allow the assessment of the effects of different drugs on interstitial fibrosis in hypertensive patients.

Recently published investigations for the first time reported the beneficial effect of antihypertensive drugs on LV global longitudinal strain in hypertensive patients followed for 6 and 12 months, respectively, after introduction of antihypertensive therapy (169,170). The authors reported significant improvement of LV global longitudinal strain as well as parameters of LV diastolic function, and in this way showed that mild deterioration of LV function is reversible with appropriate and timely introduced therapy.

### PROGNOSTIC VALUE OF CHANGE OF LV MASS DURING TREATMENT

In hypertensive patients, LVH may predict the occurrence of cardiovascular events, including myocardial infarction, stroke, sudden death and heart failure. The incidence of atrial fibrillation and of renal events, such as creatinine doubling, estimated glomerular filtration rate <30 mL/min/1.73 m<sup>2</sup> or end-stage renal disease, are higher in the presence of LVH (171).

Changes of LVM index during treatment, and not only the baseline value of LVM, may have prognostic relevance (172). In the prospective randomized clinical study (LIFE), it was shown that in patients with electrocardiographic LVH, the absence of LVH during treatment was associated with a lower incidence of cardiovascular events, while the opposite was true for patients with no regression of LVH induced by long-term antihypertensive therapy (173). Several other studies have confirmed the results of the LIFE study; these studies were performed in cohorts of hypertensive patients with different demographic and clinical characteristics, with and without LVH at baseline, treated according to the decision of their general practitioner (Figure 29.4) (172,174–176).

Regression of LVH may have a prognostic significance independent of blood pressure values, even when measured by 24-hour BP. Changes in LVM and in renal function may independently predict the occurrence of cardiovascular events (176).

During antihypertensive treatment, the modifications of LV geometry, left atrial size, midwall FS and diastolic dysfunction parameters have been also shown to be associated with the incidence of cardiovascular events independent of LVM change.

Therefore, although it must not be considered an absolute indication, in a patient with LVH at baseline it is recommended to repeat an echocardiogram after 12 months of treatment, for the great amount of given information (45). During this time interval, the probability that the degree of anatomic and/or functional changes indicates a real biological modification is greatest.

In conclusion, in hypertensive patients, regression of LVH together with optimal BP control is associated with a reduced incidence of myocardial ischemia, arrhythmias and heart failure and therefore should be considered a specific goal of antihypertensive treatment.



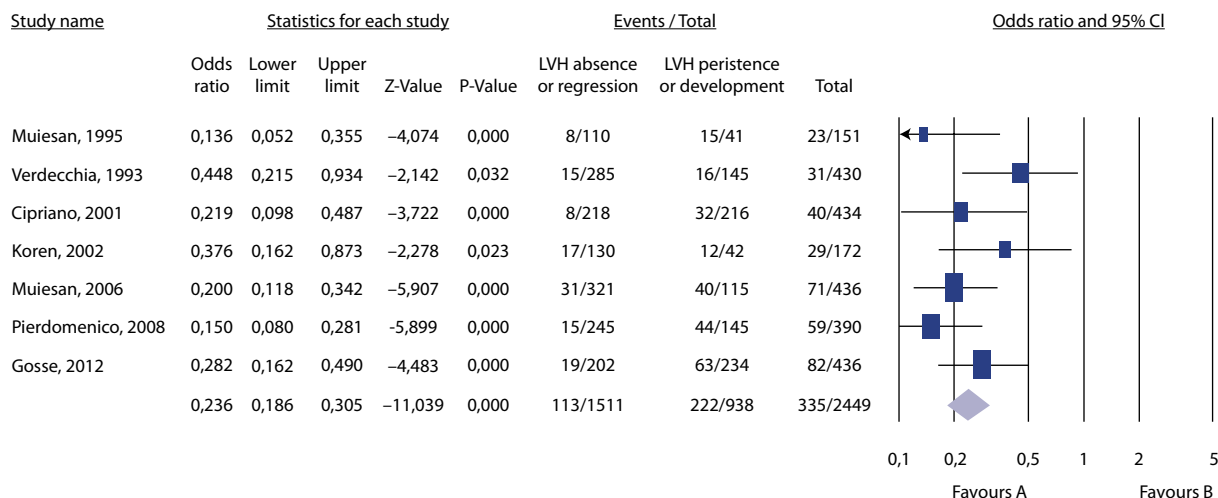


**Figure 29.4** Studies evaluating the occurrence of CV events in hypertensive patients according to changes in LV mass. (Wachtell et al. *J Hypertens* 2010; 28(7): 1541–1546; Thomopoulos et al. *J Hypertens*. 2016 March; 34(3): 373–384. Agabiti-Rosei E, Muiesan ML. In: Agabiti-Rosei, Mancia (eds). *Assessment of Preclinical Organ Damage in Hypertension*. 2015, Springer-Verlag.)

## REFERENCES

- Kannel WB. Prevalence and natural history of electrocardiographic left ventricular hypertrophy. *Am J Med* 1983; 75(Suppl. A): 4–11.
- Vasan RS, Levy D. The role of hypertension in the pathogenesis of heart failure: A clinical mechanistic overview. *Arch Intern Med* 1996; 156: 1789–1796.
- Hunt SA, Abraham WT, Chin MH et al. American College of Cardiology; American Heart Association Task Force on Practice Guidelines; American College of Chest Physicians; International Society for Heart and Lung Transplantation; Heart Rhythm Society. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2005; 112: e154–e235.
- Gunther S, Grossman W. Determinants of ventricular function in pressure-overload hypertrophy. *Circulation* 1979; 59: 679–688.
- Shimizu I, Minamino T. Physiological and pathological hypertrophy. *J Mol Cell Cardiol* 2016; 97: 245–262.
- Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium: Fibrosis and renin-angiotensin-aldosterone system. *Circulation* 1991; 83: 1849–1853.
- Weber KT. Collagen matrix synthesis and degradation in the development and regression of left ventricular hypertrophy. *Cardiovasc Res* 1991; 12: 61–69.
- Gonzalez A, Ravassa S, Lopez B et al. Myocardial remodeling in hypertension. *Hypertension* 2018; 72: 549–558.
- Hunter JJ, Chien KR. Signaling pathways for cardiac hypertrophy and failure. *N Engl J Med* 1999; 341: 1276–1283.
- Devereux RB. Hypertensive cardiac hypertrophy, pathophysiology and clinical characteristics. In: Laragh JH, Brenner BM (eds). *Hypertension, Pathophysiology, Diagnosis and Management*. 2nd ed. Raven Press, New York; 1995.
- Drazner M. The progression of hypertensive heart disease. *Circulation* 2011; 123: 327–334.
- Gosse P, Ansoborlo P, Jullien VV et al. Ambulatory blood pressure and left ventricular hypertrophy. *Blood Press Monit* 1997; 2: 70–74.
- Parati G, Pomidossi G, Albini F et al. Relationship of 24-hour blood pressure mean and variability to severity of target-organ damage in hypertension. *J Hypertens* 1987; 5: 93–98.
- Rizzoni D, Muiesan ML, Montani G et al. Relationship between initial cardiovascular structural changes and daytime and nighttime blood pressure monitoring. *Am J Hypertens* 1992; 5: 180–186.
- Gatzka CD, Schmieder RE, Schobel HP et al. Improved prediction of left ventricular mass from ambulatory blood pressure monitoring using average tension-time index. *J Hypertens Suppl* 1993; 11: S98–S99.
- Cuspidi C, Meani S, Salerno M et al. Cardiovascular target organ damage in essential hypertensives with or without reproducible nocturnal fall in blood pressure. *J Hypertens* 2004; 22: 273–280.
- Mancia G, Zanchetti A, Agabiti-Rosei E et al. Ambulatory blood pressure is superior to clinic blood pressure in predicting treatment-induced regression of left ventricular hypertrophy. SAMPLE Study Group. Study on Ambulatory Monitoring of Blood Pressure and Lisinopril Evaluation. *Circulation* 1997; 95: 1464–1670.
- Devereux RB, Pickering TG, Harshfield GA et al. Left ventricular hypertrophy in patients with hypertension: Importance of blood pressure response to regularly recurring stress. *Circulation* 1983; 68: 470–476.
- Agabiti-Rosei E, Mancia G, O'Rourke MF et al. Central blood pressure measurements and antihypertensive therapy: A consensus document. *Hypertension* 2007; 50: 154–160.
- Wang KL, Cheng HM, Chuang SY et al. Central or peripheral systolic or pulse pressure: Which best relates to target organs and future mortality? *J Hypertens* 2009; 27: 461–467.
- Roman MJ, Devereux RB, Kizer JR et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: The Strong Heart Study. *Hypertension* 2007; 50: 197–203.
- Roman MJ and Devereux RB. Association of central and peripheral blood pressures with intermediate cardiovascular phenotypes. *Hypertension* 2014; 63: 1148–1153.
- Weber T, Wassertheurer S, Schmidt-Trucksäss A et al. Relationship between 24-hour ambulatory central-systolic blood pressure and left ventricular mass: A prospective multicenter study. *Hypertension* 2017; 70(6): 1157–1164.
- Lauer MS, Anderson KM, Levy D. Separate and joint influences of obesity and mild hypertension on left ventricular mass and geometry: The Framingham Heart Study. *J Am Coll Cardiol* 1992; 19: 130–134.
- Schmieder RE, Messerli FH. Does obesity influence early target organ damage in hypertensive patients? *Circulation* 1993; 87: 1482–1488.
- de Simone G, Devereux RB, Roman MJ et al. Relation of obesity and gender to left ventricular hypertrophy in normotensive and hypertensive adults. *Hypertension* 1994; 23: 600–606.
- Schmieder RE, Messerli FH. Hypertension and the heart. *J Hum Hypertens* 2000; 14: 597–604.
- Schmieder RE, Messerli FH, Garavaglia GE, Nunez BD. Dietary salt intake. A determinant of cardiac involvement in essential hypertension. *Circulation* 1988; 78: 951–956.
- Daniels SD, Meyer RA, Loggie JM. Determinants of cardiac involvement in children and adolescents with essential hypertension. *Circulation* 1990; 82: 1243–1248.
- Takeda Y, Yoneda T, Demura M et al. Sodium-induced cardiac aldosterone synthesis causes cardiac hypertrophy. *Endocrinology* 2000; 141: 1901–1904.

31. Levy D, Anderson KM, Savage DD et al. Echocardiographically detected left ventricular hypertrophy: Prevalence and risk factors. The Framingham Heart Study. *Ann Intern Med* 1988; 108: 7–13.
32. Drazner MH, Dries DL, Peshock RM et al. Left ventricular hypertrophy is more prevalent in blacks than whites in the general population: The Dallas Heart Study. *Hypertension* 2005; 46: 124–129.
33. Post WS, Larson MG, Myers RH et al. Heritability of left ventricular mass: The Framingham Heart Study. *Hypertension* 1997; 30: 1025–1028.
34. Schlaich MP, Kaye DM, Lambert E et al. Relation between cardiac sympathetic activity and hypertensive left ventricular hypertrophy. *Circulation* 2003; 108: 560–565.
35. Greenwood JP, Scott EM, Stoker JB, Mary DA. Hypertensive left ventricular hypertrophy: Relation to peripheral sympathetic drive. *J Am Coll Cardiol* 2001; 38: 1711–1717.
36. Hermida N, Michel L, Esfahani H et al. Cardiac myocyte  $\beta_3$ -adrenergic receptors prevent myocardial fibrosis by modulating oxidant stress-dependent paracrine signaling. *Eur Heart J* 2018; 39(10): 888–898.
37. Schlaich MP, Schobel HP, Hilgers K, Schmieder RE. Impact of aldosterone on left ventricular structure and function in young normotensive and mildly hypertensive subjects. *Am J Cardiol* 2000; 85: 1199–1206.
38. Schmieder RE, Langenfeld MR, Friedrich A et al. Angiotensin II related to sodium excretion modulates left ventricular structure in human essential hypertension. *Circulation* 1996; 94: 1304–1309.
39. Schlaich MP, Schobel HP, Langenfeld MR et al. Inadequate suppression of angiotensin II modulates left ventricular structure in humans. *Clin Nephrol* 1998; 49: 153–159.
40. Schmieder RE, Erdmann J, Delles C et al. Effect of the angiotensin II type 2-receptor gene (+1675 G/A) on left ventricular structure in humans. *J Am Coll Cardiol* 2001; 37: 175–182.
41. Vasan RS, Larson MG, Levy D et al. Distribution and categorization of echocardiographic measurements in relation to reference limits: The Framingham Heart Study: Formulation of a height- and sex-specific classification and its prospective validation. *Circulation* 1997; 96: 1863–1873.
42. Moser M, Hebert PR. Prevention of disease progression, left ventricular hypertrophy and congestive heart failure in hypertension treatment trials. *J Am Coll Cardiol* 1996; 27: 1214–1218.
43. Levy D, Larson MG, Vasan RS et al. The progression from hypertension to congestive heart failure. *JAMA* 1996; 275: 1557–1562.
44. Levy D, Kenchaiah S, Larson MG et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002; 347: 1397–1400.
45. Williams B, Mancia G, Spiering W et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *J Hypertens* 2018; 36: 1953–2041.
46. Wright JT Jr, Williamson JD, Whelton PK et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; 373: 2103–2116.
47. Muiesan ML, Salvetti M, Di Castelnuovo A et al. Obesity and ECG left ventricular hypertrophy. *J Hypertens* 2017; 35(1): 162–169.
48. Leibowitz D, Planer D, Ben-Ibgi F et al. Measurement of wall thickness alone does not accurately assess the presence of left ventricular hypertrophy. *Clin Exp Hypertens* 2007; 29(2): 119–125.
49. Barbieri A, Bursi F, Mantovani F et al. Left ventricular hypertrophy reclassification and death: Application of the Recommendation of the American Society of Echocardiography/European Association of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2012; 13(1): 109–117.
50. Devereux RB, Alonso DR, Lutas EM et al. Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. *Am J Cardiol* 1986; 57(6): 450–458.
51. Reichek N, Devereux RB. Left ventricular hypertrophy: Relationship of anatomic, echocardiographic and electrocardiographic findings. *Circulation* 1981; 63(6): 1391–1398.
52. Lang RM, Badano LP, Mor-Avi V et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; 28: 1–39 e14.
53. Gosse P, Jullien V, Jarnier P et al. Echocardiographic definition of left ventricular hypertrophy in the hypertensive: Which method of indexation of left ventricular mass? *J Hum Hypertens* 1999; 13(8): 505–509.
54. de Simone G, Daniels SR, Devereux RB et al. Left ventricular mass and body size in normotensive children and adults: Assessment of allometric relations and impact of overweight. *J Am Coll Cardiol* 1992; 20(5): 1251–1260.
55. Chirinos JA, Segers P, De Buyzere ML et al. Left ventricular mass: Allometric scaling, normative values, effect of obesity, and prognostic performance. *Hypertension* 2010; 56(1): 91–98.
56. Poppe KK, Doughty RN, Whalley GA. Redefining normal reference ranges for echocardiography: A major new individual person data meta-analysis. *Eur Heart J Cardiovasc Imaging* 2013; 14(4): 347–348.
57. Ganau A, Devereux RB, Roman MJ et al. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. *J Am Coll Cardiol* 1992; 19(7): 1550–1558.
58. Linzbach AJ. Heart failure from the point of view of quantitative anatomy. *Am J Cardiol* 1960; 5: 370–382.
59. Muiesan ML, Salvetti M, Monteduro C et al. Left ventricular concentric geometry during treatment adversely affects cardiovascular prognosis in hypertensive patients. *Hypertension* 2004; 43(4): 731–738.
60. Verdecchia P, Schillaci G, Borgioni C et al. Adverse prognostic significance of concentric remodeling of the left ventricle in hypertensive patients with normal left ventricular mass. *J Am Coll Cardiol* 1995; 25(4): 871–878.
61. Cuspidi C, Giudici V, Meani S et al. Extracardiac organ damage in essential hypertensives with left ventricular concentric remodeling. *J Hum Hypertens* 2010; 24(6): 380–386.
62. Bang CN, Gerds E, Aurigemma GP et al. Four-group classification of left ventricular hypertrophy based on ventricular concentricity and dilatation identifies a low-risk subset of eccentric hypertrophy in hypertensive patients. *Circ Cardiovasc Imaging* 2014; 7(3): 422–429.
63. de Simone G, Palmieri V, Koren MJ et al. Prognostic implications of the compensatory nature of left ventricular mass in arterial hypertension. *J Hypertens* 2001; 19(1): 119–125.
64. Muiesan ML, Salvetti M, Painsi A et al. Inappropriate left ventricular mass changes during treatment adversely affects cardiovascular prognosis in hypertensive patients. *Hypertension* 2007; 49: 1077–1083.
65. de Simone G, Gottdiener JS, Chinali M, Maurer MS. Left ventricular mass predicts heart failure not related to previous myocardial infarction: The Cardiovascular Health Study. *Eur Heart J* 2008; 29: 741–747.
66. de Simone G, Muiesan ML, Ganau A et al. Reliability and limitations of echocardiographic measurement of left ventricular mass for risk stratification and follow-up in single patients: The RES trial. Working Group on Heart and Hypertension of the Italian Society of Hypertension. Reliability of M-mode Echocardiographic Studies. *J Hypertens* 1999; 17(12 Pt 2): 1955–1963.
67. Muiesan ML, de Simone G, Ganau A et al. Inappropriate left ventricular mass: Reliability and limitations of echocardiographic measurement for risk stratification and follow-up in single patients. *J Hypertens* 2006; 24(11): 2293–2298.
68. Schillaci G, Verdecchia P, Porcellati C et al. Continuous relation between left ventricular mass and cardiovascular risk in essential hypertension. *Hypertension* 2000; 35(2): 580–586.
69. Yasuno S, Ueshima K, Oba K et al. Clinical significance of left ventricular hypertrophy and changes in left ventricular mass in high-risk hypertensive patients: A subanalysis of the Candesartan Antihypertensive Survival Evaluation in Japan trial. *J Hypertens* 2009; 27(8): 1705–1712.
70. Cuspidi C, Facchetti R, Sala C et al. Normal values of left-ventricular mass: Echocardiographic findings from the PAMELA study. *J Hypertens* 2012; 30(5): 997–1003.
71. Kusunose K, Kwon DH, Motoki H et al. Comparison of three-dimensional echocardiographic findings to those of magnetic resonance imaging for determination of left ventricular mass in patients with ischemic and non-ischemic cardiomyopathy. *Am J Cardiol* 2013; 112(4): 604–611.
72. Mizukoshi K, Takeuchi M, Nagata Y et al. Normal values of left ventricular mass index assessed by transthoracic three-dimensional echocardiography. *J Am Soc Echocardiogr* 2016; 29: 51–61.
73. Bonow RO, Udelson JE. Left ventricular diastolic dysfunction as a cause of congestive heart failure. Mechanisms and management. *Ann Intern Med* 1992; 117: 502–510.
74. Cregler LL, Georgiou D, Sosa I. Left ventricular diastolic dysfunction in patients with congestive heart failure. *J Natl Med Assoc* 1991; 83: 49–52.

75. Brogan WCD, Hillis LD, Flores ED, Lange RA. The natural history of isolated left ventricular diastolic dysfunction. *Am J Med* 1992; 92: 627–630.
76. Mandinov L, Eberli FR, Seiler C, Hass OM. Diastolic heart failure. *Cardiovasc Res* 2000; 45: 813–825.
77. Agabiti-Rosei E, Muiesan ML. Hypertension and diastolic function. *Drugs* 1993; 46(Suppl. 2): 61–67.
78. Perlini S, Chung ES, Aurigemma GP, Meyer TE. Alterations in early filling dynamics predict the progression of compensated pressure overload hypertrophy to heart failure better than abnormalities in midwall systolic shortening. *Clin Exp Hypertens* 2013; 35(6): 401–411.
79. Mor-Avi V, Lang RM, Badano LP et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *J Am Soc Echocardiogr* 2011; 24(3): 277–313.
80. Little WC, Downes TR, Applegate RJ. Invasive evaluation of left ventricular diastolic performance. *Herz* 1990; 15: 362–376.
81. Zile MR, DeSantis SM, Baicu CF et al. Plasma biomarkers that reflect determinants of matrix composition identify the presence of left ventricular hypertrophy and diastolic heart failure. *Circ Heart Fail* 2011; 4: 246–256.
82. Muiesan ML, Rizzoni D, Zulli R et al. Cardiovascular characteristics in normotensive subjects with or without family history of hypertension. *Clin Exper Hypertens* 1996; 18(7): 901–920.
83. Radice M, Alli C, Avanzino F et al. Left ventricular structure and function in normotensive adolescents with a genetic predisposition to hypertension. *Am Heart J* 1986; 111: 115–120.
84. Bella JN, Palmieri V, Liu JE et al. Relationship between left ventricular diastolic relaxation and systolic function in hypertension, the Hypertension Genetic Epidemiology Network (HyperGEN) Study. *Hypertension* 2001; 38: 424–434.
85. Cuocolo A, Sax FL, Brush JE et al. Left ventricular hypertrophy and impaired diastolic filling in essential hypertension. *Circulation* 1990; 81: 978–986.
86. Muiesan ML, Rizzoni D, Zulli R et al. Left ventricular systolic function during stress as related to impaired diastolic filling in essential hypertension. *High Blood Press* 1992; 1: 287–295.
87. Gerds E, Bjornstad H, Toft S et al. Impact of diastolic Doppler indices on exercise capacity in hypertensive patients with electrocardiographic left ventricular hypertrophy (a LIFE substudy). *J Hypertens* 2002; 20: 1223–1229.
88. Fagard R, Pardaens K. Left ventricular diastolic function predicts outcome in uncomplicated hypertension. *Am J Hypertens* 2001; 14: 504–508.
89. Kurt M, Wang J, Torre-Amione G, Nagueh SF. Left atrial function in diastolic heart failure. *Circ Cardiovasc Imaging* 2009; 2(1): 10–15.
90. Klein AL, Burstow DJ, Tajik AJ et al. Effects of age on left ventricular dimensions and filling dynamics in 117 normal persons. *Mayo Clin Proc* 1994; 69(3): 212–224.
91. Nagueh SF. Echocardiographic assessment of left ventricular relaxation and cardiac filling pressures. *Curr Heart Fail Rep* 2009; 6(3): 154–159.
92. Wang J, Nagueh SF. Echocardiographic assessment of left ventricular filling pressures. *Heart Fail Clin* 2008; 4(1): 57–70.
93. Sharp AS, Tapp RJ, Thom SA et al. Tissue Doppler E/E' ratio is a powerful predictor of primary cardiac events in a hypertensive population: An ASCOT substudy. *Eur Heart J* 2010; 31(6): 747–752.
94. Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31(7): 1281–1357.
95. Jenkins C, Chan J, Hanekom L, Marwick TH. Accuracy and feasibility of online 3-dimensional echocardiography for measurement of left ventricular parameters. *J Am Soc Echocardiogr* 2006; 19(9): 1119–1128.
96. Marwick TH. Application of 3D echocardiography to everyday practice: Development of normal ranges is step 1. *JACC Cardiovasc Imaging* 2012; 5(12): 1198–1200.
97. Miyoshi H, Oishi Y, Mizuguchi Y et al. Association of left atrial reservoir function with left atrial structural remodeling related to left ventricular dysfunction in asymptomatic patients with hypertension: Evaluation by two-dimensional speckle-tracking echocardiography. *Clin Exp Hypertens* 2015; 37: 155–165.
98. Vinch CS, Aurigemma GP, Simon HU et al. Analysis of left ventricular systolic function using midwall mechanics in patients >60 years of age with hypertensive heart disease and heart failure. *Am J Cardiol* 2005; 96(9): 1299–1303.
99. de Simone G, Devereux RB, Roman MJ et al. Assessment of left ventricular function by the midwall fractional shortening/end-systolic stress relation in human hypertension. *J Am Coll Cardiol* 1994; 23(6): 1444–1451.
100. Bella JN, Devereux RB. Left ventricular midwall function in systemic hypertension. *Cardiologia* 1998; 43(5): 465–468.
101. Muiesan ML, Salvetti M, Monteduro C et al. Changes in midwall systolic performance and cardiac hypertrophy reduction in hypertensive patients. *J Hypertens* 2000; 18: 1651–1659.
102. Perlini S, Muiesan ML, Cuspidi C et al. Midwall mechanics are improved after regression of hypertensive left ventricular hypertrophy and normalization of chamber geometry. *Circulation* 2001; 103: 678–683.
103. Diamond JA, Krakoff LR, Goldman A et al. Comparison of two calcium channel blockers on hemodynamics, left ventricular mass and coronary vasodilatory response in advanced hypertension. *Am J Hypertens* 2001; 14: 231–240.
104. Jenkins C, Bricknell K, Hanekom L, Marwick TH. Reproducibility and accuracy of echocardiographic measurements of left ventricular parameters using real-time three-dimensional echocardiography. *J Am Coll Cardiol* 2004; 44(4): 878–886.
105. Maceira AM, Mohiaddin RH. Cardiovascular magnetic resonance in systemic hypertension. *J Cardiovasc Magn Reson* 2012; 14: 28.
106. Perrone-Filardi P, Coca A, Galderisi M et al. Non-invasive cardiovascular imaging for evaluating subclinical target organ damage in hypertensive patients: A consensus paper from the European Association of Cardiovascular Imaging (EACVI), the European Society of Cardiology Council on Hypertension, and the European Society of Hypertension (ESH). *Eur Heart J Cardiovasc Imaging* 2017; 18: 945–960.
107. Celic V, Tadic M, Suzic-Lazic J et al. Two- and three-dimensional speckle tracking analysis of the relation between myocardial deformation and functional capacity in patients with systemic hypertension. *Am J Cardiol* 2014; 113(5): 832–839.
108. Tadic M, Cuspidi C, Bombelli M, Grassi G. Hypertensive heart disease beyond left ventricular hypertrophy: Are we ready for echocardiographic strain evaluation in everyday clinical practice? *J Hypertens* 2018; 36(4): 744–753.
109. Opdahl A, Helle-Valle T, Skulstad H, Smiseth OA. Strain, strain rate, torsion and twist: Echocardiographic evaluation. *Curr Cardiol Rep* 2015; 17(3): 568.
110. Lee WH, Liu YW, Yang LT, Tsai WC. Prognostic value of longitudinal strain of subepicardial myocardium in patients with hypertension. *J Hypertens* 2016; 34: 1195–1200.
111. Kim SA, Park SM, Kim MN, Shim WJ. Assessment of left ventricular function by layer-specific strain and its relationship to structural remodeling in patients with hypertension. *Can J Cardiol* 2016; 32: 211–216.
112. Tadic M, Cuspidi C, Majstorovic A et al. The relationship between left ventricular deformation and different geometric patterns according to the updated classification: Findings from the hypertensive population. *J Hypertens* 2015; 33: 1954–1961.
113. Kannel WB, Gordon T, Offutt D. Left ventricular hypertrophy by electrocardiogram: Prevalence, incidence and mortality in the Framingham study. *Ann Intern Med* 1969; 71: 89–105.
114. Kannel WB, Gordon T, Castelli WP, Margolis JR. Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease: The Framingham study. *Ann Intern Med* 1970; 72: 813–822.
115. Roman MJ, Pickering TG, Schawartz JE et al. Association of carotid atherosclerosis and left ventricular hypertrophy. *J Am Coll Cardiol* 1995; 25: 83–90.
116. Cuspidi C, Marabini M, Lonati L et al. Cardiac and carotid structure in patients with established hypertension and white-coat hypertension. *J Hypertens* 1995; 13: 1707–1711.
117. Muiesan ML, Pasini GF, Salvetti M et al. Cardiac and vascular structural changes prevalence and relation to ambulatory blood pressure in a middle-aged general population in Northern Italy, the Vobarno Study. *Hypertension* 1996; 27: 1046–1052.
118. Sihm I, Schroeder AP, Aalkjaer C et al. The relation between peripheral vascular structure, left ventricular hypertrophy and ambulatory blood pressure in essential hypertension. *Am J Hypertens* 1995; 8: 987–996.
119. Lucarini A, Spessot M, Picano E et al. Lack of correlation between cardiac mass and arteriolar structural changes in mild-to-moderate hypertension. *J Hypertens* 1991; 9: 1187–1191.
120. Rizzoni D, Muiesan ML, Porteri E et al. Relations between cardiac and vascular structure in patients with primary and secondary hypertension. *J Am Coll Cardiol* 1998; 32: 985–992.



121. Muiesan ML, Rizzoni D, Salvetti A et al. Structural changes in small resistance arteries and left ventricular geometry in patients with primary and secondary hypertension. *J Hypertens* 2002; 20: 1439–1446.
122. Pierdomenico SD, Lapenna D, Guglielmi MD et al. Vascular changes in hypertensive patients with different left ventricular geometry. *J Hypertens* 1995; 13: 1701–1706.
123. Cuspidi C, Lonati L, Sampieri L et al. Left ventricular concentric remodelling and carotid structural changes in essential hypertension. *J Hypertens* 1996; 14: 1441–1446.
124. Bikkina M, Levy D, Evans JC et al. Left ventricular mass and risk of stroke in an elderly cohort. The Framingham Heart Study. *JAMA* 1994; 272: 33–36.
125. Kozakowa M, Palombo C, Pratali L et al. Mechanisms of coronary flow reserve impairment in human hypertension. An integrated approach by transthoracic and transesophageal echocardiography. *Hypertension* 1997; 29: 551–559.
126. Niteberg A, Anthony I. Epicardial coronary arteries are not adequately sized in hypertensive patients. *J Am Coll Cardiol* 1996; 27: 115–123.
127. Rizzoni D, Palombo C, Porteri E et al. Relationship between coronary vasodilator capacity and small artery remodelling in hypertensive patients. *J Hypertens* 2003; 21: 615–621.
128. Rakusan K, Flanagan MF, Geva T et al. Morphometry of human coronary capillaries during normal growth and the effect of age on left ventricular pressure overload hypertrophy. *Circulation* 1992; 86: 38–46.
129. Picano E, Palinkas A, Amyot R. Diagnosis of myocardial ischemia in hypertensive patients. *J Hypertens* 2001; 19: 1177–1183.
130. Sicari R, Nihoyannopoulos P, Evangelista A et al. Stress Echocardiography Expert Consensus Statement--Executive Summary: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur Heart J* 2009; 30: 278–289.
131. Vatner SF, Hittinger L. Coronary vascular mechanisms involved in decompensation from hypertrophy to heart failure. *J Am Coll Cardiol* 1993; 22(Suppl. A): 34A–40A.
132. Devereux RB, Roman MJ, Palmieri V et al. Left ventricular wall stresses and wall stress-mass-heart-rate products in hypertensive patients with electrocardiographic left ventricular hypertrophy: The LIFE study. *J Hypertens* 2000; 18: 1129–1138.
133. Gunnig IF, Cooper G, Harrison CE, Coleman HN. Myocardial oxygen consumption in experimental hypertrophy and congestive heart failure due to pressure overload. *Am J Cardiol* 1973; 32: 427–431.
134. Motz W, Vogt M, Rabenau O et al. Evidence of endothelial dysfunction in coronary resistance vessels in patients with angina pectoris and normal coronary angiograms. *Am J Cardiol* 1991; 68: 996–1003.
135. Rudic RD, Shesely EG, Meeda N et al. Direct evidence for the importance of endothelium-derived nitric oxide in vascular remodelling. *J Clin Invest* 1998; 101: 731–736.
136. Messerli FH, Ventura HO, Elizardi DJ et al. Hypertension and sudden death. Increased ventricular ectopic activity in left ventricular hypertrophy. *Am J Med* 1984; 77: 18–22.
137. Kannel WB, McGee DL, Schatzkin A. An epidemiological perspective of sudden death. 26-year follow-up in the Framingham Study. *Drugs* 1984; 28: 1–16.
138. Bikkina M, Larson MG, Levy D. Asymptomatic ventricular arrhythmias and mortality risk in subjects with left ventricular hypertrophy. *J Am Coll Cardiol* 1993; 22: 1111–1116.
139. McLennan JM, Henderson E, Morris KI, Dargie HJ. Ventricular arrhythmias in patients with hypertensive left ventricular hypertrophy. *N Engl J Med* 1987; 317: 787–792.
140. Bayes-Genis A, Guindo J, Vinolas X et al. Cardiac arrhythmias and left ventricular hypertrophy in systemic hypertension and their influences on prognosis. *Am J Cardiol* 1995; 76: 54D–59D.
141. Messerli FH. Hypertension and sudden cardiac death. *Am J Hypertens* 1999; 12: 181S–188S.
142. Siegel D, Black DM, Seeley DG, Hulley SB. Circadian variation in ventricular arrhythmias in hypertensive men. *Am J Cardiol* 1992; 69: 344–347.
143. Aronow WS, Epstein S, Koenigsberg M, Schwartz KS. Usefulness of echocardiographic left ventricular hypertrophy, ventricular tachycardia and complex ventricular arrhythmias in predicting ventricular fibrillation or sudden cardiac death in elderly patients. *Am J Cardiol* 1988; 62: 1124–1125.
144. Gonzalez-Fernandez RA, Rivera M, Rodriguez PJ et al. Prevalence of ectopic ventricular activity after left ventricular mass regression. *Am J Hypertens* 1993; 6: 308–313.
145. Wachtell K, Okin PM, Olsen MH et al. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive therapy and reduction in sudden cardiac death: The LIFE Study. *Circulation* 2007; 116: 700–705.
146. Hollifield JW. Potassium and magnesium abnormalities: Diuretics and arrhythmias in hypertension. *Am J Med* 1984; 77: 28–32.
147. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: The Framingham Study. *N Engl J Med* 1982; 306: 1018–1022.
148. Verdecchia P, Reboldi G, Gattobigio R et al. Atrial fibrillation in hypertension: Predictors and outcome. *Hypertension* 2003; 41: 218–223.
149. Wachtell K, Lehto M, Gerds E et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: The Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. *J Am Coll Cardiol* 2005; 45: 712–719.
150. Van Noord T, Tieleman RG, Bosker HA et al. Beta-blockers prevent subacute recurrences of persistent atrial fibrillation only in patients with hypertension. *Europace* 2004; 6: 343–350.
151. Schmieder R, Kjeldsen S, Julius S et al. Reduced incidence of new onset atrial fibrillation with angiotensin II receptor blockade: The Value-Trial. *J Hypertens* 2006; 24(Suppl 1): S3.
152. Ehrlich JR, Hohnloser SH, Nattel S. Role of angiotensin system and effects of its inhibition in atrial fibrillation: Clinical and experimental evidence. *Eur Heart J* 2006; 27: 512–518.
153. Healey JS, Baranchuk A, Crystal E et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: A meta-analysis. *J Am Coll Cardiol* 2005; 45: 1832–1839.
154. L'Allier PL, Ducharme A, Keller PF et al. Angiotensin-converting enzyme inhibition in hypertensive patients is associated with a reduction in the occurrence of atrial fibrillation. *J Am Coll Cardiol* 2004; 44: 159–164.
155. Madrid AH, Bueno MG, Rebollo JM et al. Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation: A prospective and randomized study. *Circulation* 2002; 106: 331–336.
156. Ueng KC, Tsai TP, Yu WC et al. Use of enalapril to facilitate sinus rhythm maintenance after external cardioversion of long-standing persistent atrial fibrillation. Results of a prospective and controlled study. *Eur Heart J* 2003; 24: 2090–2098.
157. Verdecchia P, Dagenais G, Healey J et al. Blood pressure and other determinants of new-onset atrial fibrillation in patients at high cardiovascular risk in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant subjects with cardiovascular Disease studies. *J Hypertens* 2012; 30: 1004–1014.
158. Gavras I, Gavras H. The antiarrhythmic potential of angiotensin II antagonism: Experience with losartan. *Am J Hypertens* 2000; 13: 512–517.
159. Schmieder RE, Hilgers KF, Schlaich MP, Schmidt BMW. Renin-angiotensin system and cardiovascular risk. *Lancet* 2007; 369: 1208–1219.
160. Boos CJ, Anderson RA, Lip GY. Is atrial fibrillation an inflammatory disorder? *Eur Heart J* 2006; 27: 136–149.
161. Schneider MP, Hua TA, Böhm M et al. Prevention of atrial fibrillation by renin-angiotensin system inhibition a meta-analysis. *J Am Coll Cardiol* 2010; 55: 2299–2307.
162. Manolis AJ, Agabiti Rosei E, Coca A et al. Hypertension and atrial fibrillation: Diagnostic approach, prevention and treatment. Position paper of the Working Group 'Hypertension Arrhythmias and Thrombosis' of the European Society of Hypertension. *J Hypertens* 2012; 30: 239–252.
163. Cuspidi C, Sala C, Negri F et al. Prevalence of left-ventricular hypertrophy in hypertension: An updated review of echocardiographic studies. *J Hum Hypertens* 2012; 26(6): 343–349.
164. Fagard RH, Celis H, Thijs L, Wouters S. Regression of left ventricular mass by antihypertensive treatment: A meta-analysis of randomized comparative studies. *Hypertension* 2009; 54(5): 1084–1091.
165. de Simone G, Devereux RB, Izzo R et al. Lack of reduction of left ventricular mass in treated hypertension: The strong heart study. *J Am Heart Assoc* 2013; 2(3): e000144.
166. Mancusi C, Gerds E, De Simone G et al. Impact of isolated systolic hypertension on normalization of left ventricular structure during antihypertensive treatment (the LIFE study). *Blood Press* 2014; 23(4): 206–212.
167. Wachtell K, Dahlöf B, Rokkedal J et al. Change of left ventricular geometric pattern after 1 year of antihypertensive treatment: The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study. *Am Heart J* 2002; 144(6): 1057–1064.

168. Barron AJ, Hughes AD, Sharp A et al. Long-term antihypertensive treatment fails to improve E/e' despite regression of left ventricular mass: An Anglo-Scandinavian cardiac outcomes trial substudy. *Hypertension* 2014; 63(2): 252–258.
169. Cheng S, Shah AM, Albusu JP et al. Reversibility of left ventricular mechanical dysfunction in patients with hypertensive heart disease. *J Hypertens* 2014; 32: 2479–2486.
170. Uziebło-Życzkowska B, Krzesinski P, Gielerak G, Skrobowski A. Speckle tracking echocardiography and tissue Doppler imaging reveal beneficial effect of pharmacotherapy in hypertensives with asymptomatic left ventricular dysfunction. *J Am Soc Hypertens* 2017; 11: 334–342.
171. Tsioufis C, Kokkinos P, Macmanus C et al. Left ventricular hypertrophy as a determinant of renal outcome in patients with high cardiovascular risk. *J Hypertens* 2010; 28(11): 2299–2308.
172. Verdecchia P, Angeli F, Borgioni C et al. Changes in cardiovascular risk by reduction of left ventricular mass in hypertension: A meta-analysis. *Am J Hypertens* 2003; 16(11 Pt 1): 895–899.
173. Devereux RB, Wachtell K, Gerdts E et al. Prognostic significance of left ventricular mass change during treatment of hypertension. *JAMA* 2004; 292(19): 2350–2356.
174. Muiesan ML, Salvetti M, Rizzoni D et al. Association of change in left ventricular mass with prognosis during long-term antihypertensive treatment. *J Hypertens* 1995; 13(10): 1091–1095.
175. Gosse P, Cremer A, Vircoulon M et al. Prognostic value of the extent of left ventricular hypertrophy and its evolution in the hypertensive patient. *J Hypertens* 2012; 30(12): 2403–2409.
176. Salvetti M, Muiesan ML, Paini A et al. Left ventricular hypertrophy and renal dysfunction during antihypertensive treatment adversely affect cardiovascular prognosis in hypertensive patients. *J Hypertens* 2012; 30(2): 411–420.
177. Wachtell K, Gerdts E, Palmieri V et al. In-treatment midwall and endocardial fractional shortening predict cardiovascular outcome in hypertensive patients with preserved baseline systolic ventricular function: The Losartan Intervention For Endpoint reduction study. *J Hypertens* 2010; 28(7): 1541–1546.
178. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure-lowering treatment. 6. Prevention of heart failure and new-onset heart failure—meta-analyses of randomized trials. *J Hypertens*. 2016 March; 34(3): 373–384.
179. Nagueh SF, Smiseth OA, Appleton CP. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the american society of echocardiography and the european association of cardiovascular imaging. *J Am Soc Echocardiogr* 2016; 29: 277–314.
180. Agabiti-Rosei E, Muiesan ML. In: Agabiti-Rosei, Mancia (eds). *Assessment of Preclinical Organ Damage in Hypertension*. 2015, Springer-Verlag.



*Cristina Sierra, Miguel Camafort and Antonio Coca*

## INTRODUCTION

Hypertension is the most prevalent cardiovascular (CV) risk factor and the main risk factor for cerebral macrovascular complications such as stroke, and microvascular complications such as white matter lesions (WML), lacunar infarcts (LI) and microbleeds, which are frequently silent (1,2). In addition, it has been suggested that cerebral microvascular disease contributes to vascular cognitive impairment and dementia (3) (Figure 30.1). The mechanisms underlying hypertension-related cognitive changes are complex and not yet fully understood. There has been longstanding interest in a possible cause-and-effect relationship between elevated blood pressure (BP) and cognitive outcomes. The relationship has been debated over time and continues to be a focus of controversy, especially in terms of BP lowering as a means of preventing cognitive decline or dementia (1). Despite the uncertainty surrounding the benefits of BP lowering in preventing cognitive decline or dementia, there is mounting mechanistic and epidemiologic evidence that links elevated BP to loss of cognition (1).

Functional and structural abnormalities due to hypertension may be detected in neurologically asymptomatic individuals by computerized tomography (CT), magnetic resonance imaging (MRI), transcranial Doppler (TCD) ultrasound, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) (4). Neuropsychological tests may also provide useful information. However, availability and cost considerations do not allow the widespread use of MRI in the search for asymptomatic structural organ damage in middle-aged and elderly hypertensives. Likewise, availability, cost and radiation hazards are disadvantages of techniques investigating hemodynamic abnormalities (PET, SPECT). TCD could be useful in investigating cerebral hemodynamics in hypertensive individuals, although there are not sufficient longitudinal studies to assess its predictive value.

## PATHOPHYSIOLOGY OF VASCULAR CEREBRAL DAMAGE IN ESSENTIAL HYPERTENSION

The brain is highly vulnerable to the deleterious effects of elevated BP. Systolic and diastolic hypertension in both men and women are well-established risk factors for ischaemic and haemorrhagic stroke (1,2). Hypertension is a major risk factor for two distinct types of vascular problems: the complications of atherosclerosis, including cerebral infarction, on the one hand, and the complications of hypertensive small vessel disease, including intracerebral haemorrhage, lacunar infarctions and cerebral WML, on the other hand. In some cases, some of these lesions, such as microbleeds, lacunar infarcts and cerebral WML, may be silent and only detectable by radiological findings.

In the development and progression of chronic BP elevation, hypertensive cerebral angiopathy occurs, as do secondary reparative changes and adaptive processes at all structural and functional levels of the cerebral vascular system (Table 30.1). Hypertension causes marked adaptive changes in the cerebral circulation, including increased brain vessel resistance and loss of the physiological mechanism of autoregulation. Tables 30.1 and 30.2 summarize the possible underlying pathological processes in early cerebrovascular damage and their association with functional changes.

As mentioned, there are four main signs of cerebral small vessel disease that may appear as a result of hypertension and can be detected and seen by MRI: WML, cerebral microbleeds (CMB), LI and enlarged perivascular spaces (EPS).

*White matter lesions:* Microvascular alterations caused by hypertension may lead to hypoperfusion, hypoxia and ischemia in the terminal distributions of the affected vessels (3). When these territories contain white matter, this process may alter it and cause a loss of myelin. These WML can then be seen as hyperintensities in T2-weighted MRI

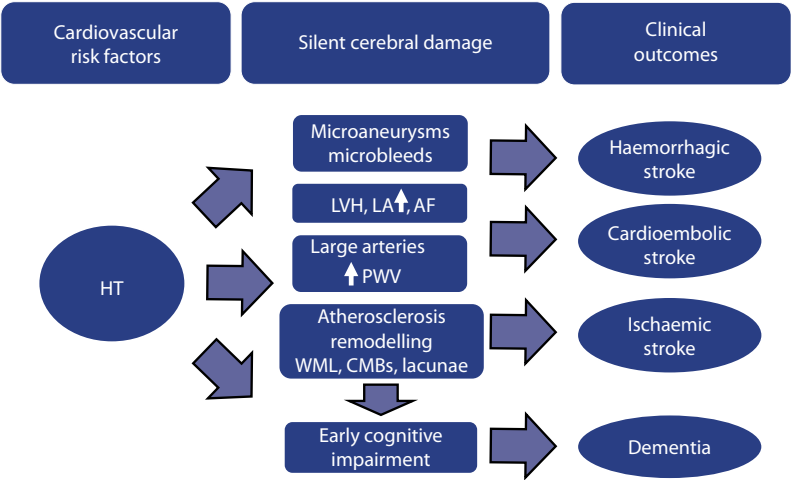


**Figure 30.1** Pathophysiological mechanisms leading from hypertension to silent brain damage, and clinical outcomes. HT, hypertension; LVH, left ventricular hypertrophy; LA, left atrium; AF, atrial fibrillation; PWV, pulse wave velocity.

**Table 30.1** Main pathophysiological cerebrovascular changes associated with sustained blood pressure elevation

|                                                                               |
|-------------------------------------------------------------------------------|
| Mechanical stress (endothelial lesion)                                        |
| Endothelial dysfunction (loss of vasodilatory capacity)                       |
| Increased vascular permeability                                               |
| Opened ionic channels                                                         |
| Hypertrophy of smooth muscle vascular vessels (reduced lumen)                 |
| Contraction of smooth muscle vascular vessels (increased vascular resistance) |
| Synthesis of collagen fibre (vascular stiffness)                              |
| Transudation of plasmatic products to the arterial wall                       |

**Table 30.2** Early cerebrovascular damage associated with hypertension

|                                                                                                                                           |
|-------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Functional abnormalities</i>                                                                                                           |
| Reduced cerebral blood flow                                                                                                               |
| Increased cerebrovascular resistance                                                                                                      |
| Reduced cerebral vasomotor reactivity                                                                                                     |
| Incipient cognitive impairment                                                                                                            |
| <i>Structural abnormalities</i>                                                                                                           |
| Vascular remodelling                                                                                                                      |
| Lacunar infarct: Small deep infarcts caused by penetrating arteriolar occlusive disease                                                   |
| White matter lesions: Periventricular and subcortical white matter lesions caused by subcortical hypertensive small vessel disease        |
| Microbleeds: Punctate haemorrhagic lesions seen as homogeneous foci in the brain parenchyma of low signal intensity on T2-weighted images |

images (Figure 30.2). Large artery stiffening and endothelial dysfunction correlate with cognitive impairment and WML in elderly hypertensive subjects who present with memory complaints, and the severity of WML is inversely associated with memory function scores (5).

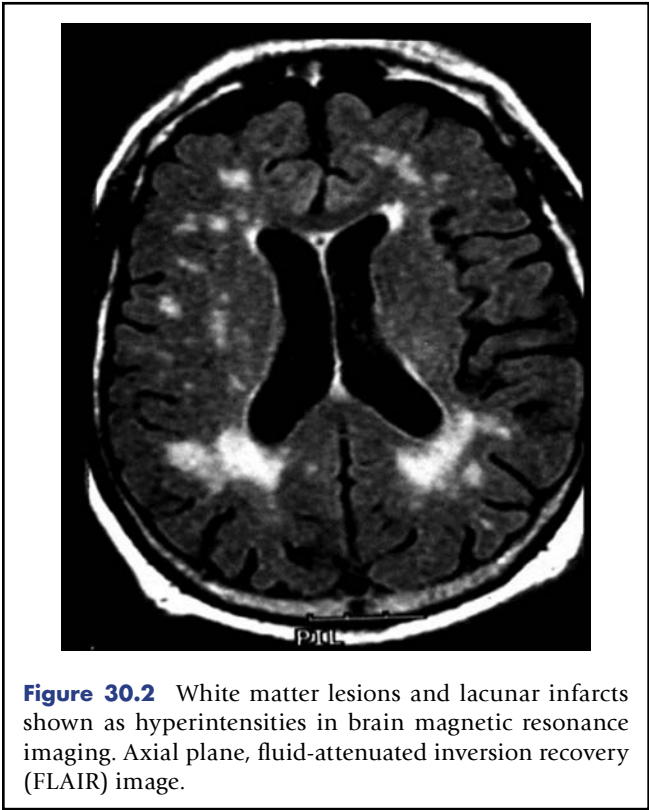


**Figure 30.2** White matter lesions and lacunar infarcts shown as hyperintensities in brain magnetic resonance imaging. Axial plane, fluid-attenuated inversion recovery (FLAIR) image.

**Cerebral microbleeds:** CMB are haemorrhagic lesions reflecting both ischaemic and haemorrhagic brain vasculopathy (Figure 30.3). They represent another sign of hypertension-related cerebral small vessel disease. They also participate as vascular factors in neurodegenerative disorders and can be seen on MRI, where they are defined as punctate homogeneous foci in the brain parenchyma of low signal intensity on T2-weighted images. It has been proposed that, depending on the location in the brain, CMB might have different aetiologies. Lobar microbleeds are seen in cerebral amyloid

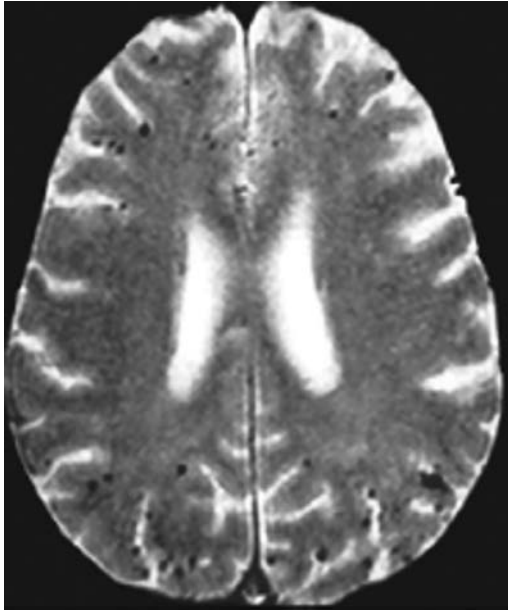


**Figure 30.3** Microbleeds shown as punctate hypointensities in frontal and occipital areas in brain magnetic resonance imaging. Gradient-echo sequence.

angiopathy, whereas hypertension, together with atherosclerosis, is thought to increase the risk of CMB in deep or infratentorial areas (6).

**Lacunar infarcts:** These are identified as sharply demarcated hyperintense lesions in T2-weighted images, with corresponding hypointense lesions with a hyperintense rim on FLAIR (Figures 30.2 and 30.4).

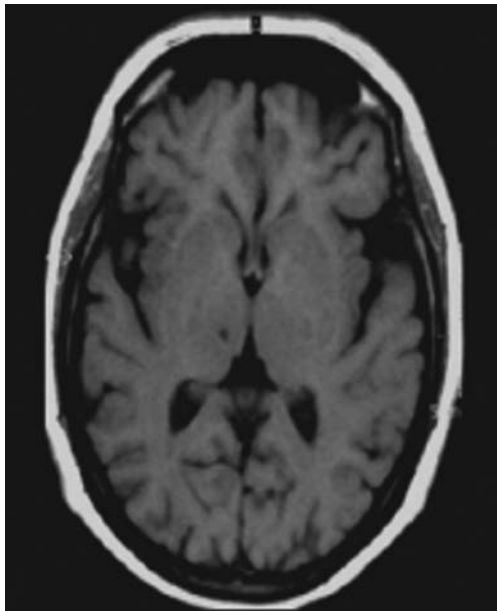


**Figure 30.4** Lacunar infarct in the right thalamus shown as a small hypointensity in brain magnetic resonance imaging. Axial plane, T1-weighted.

**Enlarged perivascular spaces:** EPS (also known as Virchow-Robin spaces) are also a marker of cerebral small vessel disease (7) and are thought to determine cognitive impairment in small vessel disease. They appear as rounded or linear-shaped lesions with a smooth margin and an absence of mass effect and are isointense to cerebrospinal fluid on T2-weighted images, but hypointense without a hyperintense rim on FLAIR images. Like LI, they frequently coexist with WML and other brain lesions.

In summary, WML, CMB, LI and EPS have all been identified as lesions which appear as a result of cerebral small vessel disease. They represent silent damage to the brain and, although they have mostly been studied individually and each has been linked to impaired cognition, they also correlate strongly with each other. A study which investigated the combined effect of these markers on different domains of cognitive function (memory, executive function, information processing speed and overall cognition) found that the accumulation of these markers of brain damage resulted in worse cognitive functioning (8). All four markers of silent damage have been linked to hypertension and cognitive function, and relationships between objective and subjective cognitive impairment have been shown (9).

## CEREBRAL AUTOREGULATION AND HIGH BLOOD PRESSURE

Autoregulation of the cerebral circulation enables the maintenance of cerebral blood flow (CBF) at constant levels despite changes in BP. Under normal conditions, autoregulation is effective at between 60 and 150 mmHg. High BP influences the cerebral circulation, causing adaptive vascular changes. Thus, hypertension influences the autoregulation of CBF by shifting both the lower and upper limits of autoregulatory capacity towards higher BP, while hypertensive patients may be especially vulnerable to episodes of hypotension (10), which may play a role in the development of silent cerebrovascular damage. Increased cerebral vascular resistance could be due to narrowing of the small vessels by lipohyalinosis and microatherosclerosis. The effect of high BP on the small vessels is well known, with vascular remodelling occurring in cerebral blood vessels during chronic hypertension. It has been suggested that this structural alteration impairs autoregulation, exposing the white matter to fluctuations in BP. For this reason, it has been hypothesized that changes in cerebral hemodynamic may play a role in the development of WML (10).

Cerebral perfusion pressure cannot be measured directly in humans. Parameters indirectly reflecting cerebral perfusion pressure are: (a) the regional CBF/regional cerebral blood volume ratio, evaluated by PET or SPECT and (b) the reactivity of the cerebral vasculature to various vasodilating stimuli ( $\text{CO}_2$ , acetazolamide), evaluated by regional CBF techniques or TCD (4).

## CEREBRAL ARTERIOSCLEROSIS

Lacunar infarction is the infarct subtype most closely and directly associated with hypertension due to its high prevalence among clinical lacunar syndromes and the

hypertensive lipohyalinotic changes seen in small penetrating vessels at necropsy (11). In other types of infarct, the effect of hypertension is less direct and is mediated by its effects on atherogenesis in large extracranial or intracranial vessels. Lacunae are small infarcts, or occasionally, haemorrhages related to Charcot-Bouchard microaneurysms.

The main current hypothesis on the association between high BP and ischaemic WML is that longstanding hypertension causes lipohyalinosis of the media and thickening of the vessel walls, with narrowing of the lumen of the small perforating arteries and arterioles that nourish the deep white matter (10). The perforating vessels, which originate in the cortical and leptomeningeal arteries, have a relatively poor anastomotic system, which makes the white matter vulnerable to cerebral ischemia. Low BP has also been reported to be a risk factor for WML (10). Hypertension may also cause disturbances in the blood-brain barrier, leading to lesions in the white matter due to cerebral oedema, the activation of astrocytes, and the effects of destructive enzymes or other poisons which pass through the damaged vessel walls (10).

Postmortem studies show that WML seen on MRI scans are associated with degenerative changes in the arterioles related to atherosclerosis, suggesting that cerebral arteriosclerosis of the penetrating vessels is the main factor in the pathogenesis of ischaemic WML (10). Several studies have reported that WML are related to atherosclerosis, as indicated by increased common carotid intima-media thickness and carotid plaques, aortic atherosclerosis in abdominal radiographs and arterial stiffness (12–14). In fact, arterial stiffness assessed using indicators such as the ankle-brachial index, pulse wave velocity, the cardio-ankle vascular index and the augmentation index, is independently associated with all components of cerebral small vessel disease including silent LI, WML and microbleeds (15).

Several vascular risk factors have been linked with WML and it seems that the greater the number of vascular risk factors for cerebrovascular disease, the greater the extent and severity of WML. A review of more than 160 studies on WML found that, in studies with a multivariate analysis, diabetes mellitus and hypertension were associated with WML, although the association with lipid abnormalities and smoking was not so clear (10). WML have also been reported to be associated with a history of stroke, LI, heart disease and atrial fibrillation, which are frequently associated with both hypertension and other vascular risk factors (10).

### ROLE OF GENETIC FACTORS IN THE PATHOGENESIS OF VASCULAR CEREBRAL DAMAGE

A family history of cerebrovascular disease and stroke is often perceived as a risk factor for stroke. The Framingham Heart Study found a positive association between a verified paternal or maternal history of stroke and an increased risk of stroke in offspring (16). Concordance rates in twin studies have shown an almost fivefold increase in stroke prevalence in monozygotic twins compared with dizygotic twins (17). However, the identification of individual causative mutations remains a challenge. The inheritance is complex, multigenic, and heterogeneous. Associations with polymorphisms have been investigated in a variety of candidate genes, including haemostatic genes, genes controlling

homocysteine metabolism and lipid metabolism, the angiotensin-converting enzyme (ACE) gene, and the endothelial nitric oxide synthase gene, with conflicting results (18) that may reflect methodological difficulties, since many studies were small and underpowered or required careful case-control matching. Robust associations between candidate genes and the occurrence of various features of cerebral small vessel disease, such as LI, intracerebral haemorrhage and WML, have not yet been established (19).

## HYPERTENSION, SMALL VESSEL DISEASE AND COGNITIVE FUNCTION

### PATHOLOGICAL ASPECTS

The mechanisms by which vascular risk factors increase the risk of cognitive impairment are not fully elucidated. As mentioned, most of these factors, and especially hypertension, have been shown to be associated with subcortical lesions seen on brain MRI: WML, LI, CMB (10,20) and EPS (21).

Pathologically, this type of small vessel disease is principally characterised by loss of smooth muscle cells from the tunica media, deposits of fibro-hyaline material, narrowing of the lumen, and thickening of the vessel wall. It is common and systemic, affects the kidneys and retinas, and is strongly associated with ageing, diabetes, and, in particular, hypertension (10). For this reason, it is also named hypertensive small vessel disease.

On the other hand, there is increasing evidence connecting cerebral hypoperfusion and neurodegeneration, specifically in Alzheimer's disease and vascular dementia (1,22). In the Rotterdam Study (23), cerebral hypoperfusion was shown to be either a risk or an aggravating factor in dementia. Chronic hypoperfusion is not only an epiphenomenon of brain tissue loss but actively promotes, initiates or accelerates neurodegeneration through multiple mechanisms, including the induction of oxidative stress, amyloid beta accumulation and aggregation, tau hyperphosphorylation, synaptic dysfunction, neuronal loss, WML and neuroinflammation (24,25).

### CHRONOPATHOLOGY

Long-term observational studies have reported that hypertension during midlife increases the risk of cognitive impairment later in life (3,26). In addition, there is some evidence that antihypertensive drug treatment could play a role in the prevention of cognitive impairment or vascular dementia through BP control (27). By contrast, the effects of late-life BP on the brain are complex and less clear. In fact, several studies, particularly in older individuals or patients at high cardiovascular risk, suggest that lower BP contributes to brain atrophy, cerebrovascular lesions and more rapid cognitive decline (28).

### CLINICAL ASPECTS

Cognitive impairment, defined as a progressive decline in some cognitive functions that does not satisfy the



diagnostic criteria of dementia, precedes at least 50% of dementia onsets. Cognitive impairment may be assessed by neuropsychological tests, as it is not necessarily evident in daily living. Cognitive decline can affect the memory or other domains (perception, abstract thought, judgment, planning ability and attention). Dementia is characterised by an intellectual deterioration that includes memory loss and one or more other neuropsychological alterations, such as apraxia, agnosia and aphasia, which interfere with social and occupational living. Mental alterations include progressive memory loss, space and temporal disorientation, loss of self-sufficiency and emotional depersonalization. The assessment of cognitive impairment requires a comprehensive cognitive battery that includes an evaluation of executive, memory, language and spatial functions.

## CEREBRAL SMALL VESSEL DISEASE AND STROKE

Stroke is the third most-frequent cause of death after cancer and heart disease in developed countries, and is one of the most common reasons for cognitive impairment and vascular dementia (29). High BP is a major risk factor for stroke, and a continuous relationship between BP and the occurrence of stroke has been established (30,31). Cerebral small vessel disease could be considered as target-organ damage of the brain due to hypertension (2). Recently published epidemiological research shows that silent cerebral small vessel disease (LI, WML, CMB) is associated with the future risk for stroke and dementia (32). It is known that WML are an important prognostic factor for stroke, cognitive impairment, dementia and death (33). Likewise, LI have also been associated with an increased risk of stroke (34,35) and cognitive impairment (36,37). Silent LI are a common finding on brain MRI in ischaemic stroke patients and increasing numbers of silent lacunae have been associated with higher incidence rates of ischaemic stroke recurrence (38). CMB have also been shown to be related to stroke (39), cognitive function and dementia (36,40), and with higher intracerebral haemorrhage recurrence (41).

## REFERENCES

- Goldstein LB, Bushnell CD, Adams RJ et al. Guidelines for the primary prevention of stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011; 42: 517–584.
- Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 36: 1281–1357.
- Sierra C, Doménech M, Camafort M, Coca A. Hypertension and mild cognitive impairment. *Curr Hypertens Rep* 2012; 14: 548–555.
- Sierra C, Doménech M, Coca A. Other techniques for neurological damage evaluation. In: Agabiti Rosei E, Mancia G. (eds). *Assessment of Preclinical Organ Damage in Hypertension*. Springer, Cham; 2015.
- Kearney-Schwartz A, Rossignol P, Bracard S et al. Vascular structure and function is correlated to cognitive performance and white matter hyperintensities in older hypertensive patients with subjective memory complaints. *Stroke* 2009; 40: 1229–1236.
- Jia Z, Mohammed W, Qiu Y et al. Hypertension increases the risk of cerebral microbleed in the territory of posterior cerebral artery: A study of the association of microbleeds categorized on a basis of vascular territories and cardiovascular risk factors. *J Stroke Cerebrovasc Dis* 2014; 23: e5–e11.
- Potter GM, Doubal FN, Jackson CA et al. Enlarged perivascular spaces and cerebral small vessel disease. *Int J Stroke* 2015; 10(3): 376–381.
- Huijts M, Duits A, van Oostenbrugge RJ et al. Accumulation of MRI markers of cerebral small vessel disease is associated with decreased cognitive function. A study in first-ever lacunar stroke and hypertensive patients. *Front Aging Neurosci* 2013; 5: 72.
- Begum A, Dewey M, Hassiotis A et al. Subjective cognitive complaints across the adult life span: A 14-year analysis of trends and associations using the 1993, 2000 and 2007 English Psychiatric Morbidity Surveys. *Psychol Med* 2014; 44: 1977–1987.
- Pantoni L. Cerebral small vessel disease: From pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol* 2010; 9: 689–701.
- Fisher CM. Lacunes: Small, deep cerebral infarcts. *Neurology* 1965; 15: 774–784.
- Bots ML, van Swieten JC, Breteler MMB et al. Cerebral white matter lesions and atherosclerosis in the Rotterdam study. *Lancet* 1993; 341: 1232–1237.
- de Leeuw FE, de Groot JC, Oudkerk M et al. Aortic atherosclerosis at middle age predicts cerebral white matter lesions in the elderly. *Stroke* 2000; 31: 425–429.
- Rundek T, Della-Morte D, Gardener H et al. Relationship between carotid arterial properties and cerebral white matter hyperintensities. *Neurology* 2017; 88: 2036–2042.
- Saji N, Toba K, Sakurai T. Cerebral small vessel disease and arterial stiffness: Tsunami effect in the brain? *Pulse (Basel)* 2016; 3: 182–189.
- Kiely DK, Wolf PA, Cupples LA et al. Familial aggregation of stroke. The Framingham Study. *Stroke* 1993; 24: 1366–1371.
- Brass LM, Isaacsohn JL, Merikangas KR, Robinette CD. A study of twins and stroke. *Stroke* 1992; 23: 221–223.
- Hassan A, Markus HS. Genetics and ischaemic stroke. *Brain* 2000; 123: 1784–1812.
- Tan R, Traylor M, Rutten-Jacobs L, Markus H. New insights into mechanisms of small vessel disease stroke from genetics. *Clin Sci (Lond)* 2017; 131: 515–531.
- Viswanathan A, Rocca WA, Tzourio C. Vascular risk factors and dementia. How to move forward? *Neurology* 2009; 72: 368–374.
- MacLulich AMJ, Wardlaw JM, Ferguson KJ et al. Enlarged perivascular spaces are associated with cognitive function in healthy elderly men. *J Neurol Neurosurg Psychiatry* 2004; 75: 1519–1523.
- Malojcic B, Giannakopoulos P, Sorond FA et al. Ultrasound and dynamic functional imaging in vascular cognitive impairment and Alzheimer's disease. *BMC Med* 2017; 15: 27.
- Ruitenberg A, den Heijer T, Bakker SL et al. Cerebral hypoperfusion and clinical onset of dementia: The Rotterdam Study. *Ann Neurol* 2005; 57: 789–794.
- Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci* 2011; 12: 723–738.
- Iadecola C. The pathobiology of vascular dementia. *Neuron* 2013; 80: 844–866.
- Sierra C, Vicario A, Escoda O. Hypertension, cognitive decline, and dementia. In: Coca A (ed). *Hypertension and Brain Damage. Updates in Hypertension and Cardiovascular Protection*. Springer, Cham; 2016.
- Rouch L, Cestac P, Hanon O et al. Antihypertensive drugs, prevention of cognitive decline and dementia: A systematic review of observational studies, randomized controlled trials and meta-analyses, with discussion of potential mechanisms. *CNS Drugs* 2015; 29: 113–130.
- Qiu C, Winblad B, Fratiglioni L. The age dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol* 2005; 4: 487–499.
- Gorelick PB, Scuteri A, Black SE et al. Vascular contributions to cognitive impairment and dementia. A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011; 42: 2672–2713.
- Multiple Risk Factor Intervention Trial. Mortality after 10 years for hypertensive participants in the Multiple Risk Factor Intervention Trial. *Circulation* 1990; 82: 1616–1628.
- MacMahon S, Peto R, Cutler J et al. Blood pressure, stroke, and coronary heart disease. Part 1: Prolonged differences in blood pressure. Prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; 355: 765–774.
- Smith EE, Saposnik G, Biessels GJ et al. Prevention of stroke in patients with silent cerebrovascular disease: A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2017; 48: e44–e71.



33. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: Systematic review and meta-analysis. *BMJ* 2010; 341: e3666.
34. Wright CB, Dong C, Perez EJ et al. Subclinical cerebrovascular disease increases the risk of incident stroke and mortality: The Northern Manhattan study. *J Am Heart Assoc* 2017; 6(9): pii: e004069.
35. Gupta A, Giambrone AE, Gialdini G et al. Silent brain infarction and risk of future stroke: A systematic review and meta-analysis. *Stroke* 2016; 47: 719–e3725.
36. Iadecola C, Yaffe K, Biller J et al. Impact of hypertension on cognitive function: A scientific statement from the American Heart Association. *Hypertension* 2016; 68: e67–e94.
37. Coca A, Monteagudo E, Doménech M et al. Can the treatment of hypertension in the middle-aged prevent dementia in the elderly? *High Blood Press Cardiovasc Prev* 2016; 23: 97–104.
38. Andersen SD, Skjøth F, Yavarian Y, Bach FW, Lip GY, Larsen TB. Multiple silent lacunes are associated with recurrent ischemic stroke. *Cerebrovasc Dis* 2016; 42: 73–80.
39. Poels MM, Ikram MA, van der Lugt A et al. Cerebral microbleeds are associated with worse cognitive function: The Rotterdam Scan Study. *Neurology* 2012; 78: 326–333.
40. Ungvari Z, Tarantini S, Kirkpatrick AC, Csiszar A, Prodan CI. Cerebral microhemorrhages: Mechanisms, consequences, and prevention. *Am J Physiol Heart Circ Physiol* 2017; 312: H1128–H1143.
41. Charidimou A, Imaizumi T, Moulin S et al. Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds: A meta-analysis. *Neurology* 2017; 89: 820–829.

# LARGE ARTERY DAMAGE: MEASUREMENT AND CLINICAL IMPORTANCE

# 31

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## INTRODUCTION

In hypertension, large arteries stiffen, and pulse pressure increases due to wave reflections. A major reason for measuring arterial stiffness 'routinely' in clinical practice in hypertensive patients comes from the recent demonstration that arterial stiffness and wave reflections have a predictive value for CV events (20,35). A large body of evidence has been published during the past decade concerning the epidemiology, pathophysiology and pharmacology of large arteries in hypertension. In particular, two expert consensus documents have reviewed the methodological agreements for measuring arterial stiffness (20,41). This chapter does not address the issues of endothelial dysfunction and intima-media thickening.

## PATHOPHYSIOLOGY OF LARGE ARTERY DAMAGE IN HYPERTENSION

### PATHOPHYSIOLOGY OF ARTERIAL STIFFNESS AND WAVE REFLECTION

Aortic stiffening accompanying age and cardiovascular risk factors is caused by various phenomena, including breaks in elastin fibres, cross-links of the elastin network, accumulation of collagen, fibrosis, inflammation, medial smooth muscle necrosis, calcifications and diffusion of macromolecules within the arterial wall (13,17). Although it is generally accepted that the major components that contribute to arterial stiffening are extracellular matrix (ECM) proteins such as elastin and collagens, a second important component is vascular smooth muscle cells (VSMCs), the role of which has been underlined more recently (17). Indeed, both VSMC contraction and changes in cell-ECM interaction, for instance through the architecture of cytoskeletal proteins and focal adhesions, can transfer the mechanical load from elastic components to stiff components, and thus increase the stiffness of the wall material.

The stiffness of large arteries, including the aorta, represents the ability of large vessels to dampen the pulsatility of ventricular ejection and to transform a pulsatile pressure

(and flow) at the ascending aorta into a continuous pressure (and flow), downstream, at the site of arterioles, in order to lower the energy expenditure of organ perfusion (31,35). With high blood pressure, ageing, and diabetes, the large arteries stiffen and pulse pressure (PP = systolic minus diastolic) increases at the site of central and peripheral arteries. Indeed, the arterial tree is approximated to a viscoelastic tube with numerous branches. Because the tube's end has a high level of resistance, waves are reflected, and retrograde waves are generated. As arterial stiffness increases, transmission velocity of both forward and reflected waves increase, which causes the reflected wave to arrive earlier in the central aorta and augment pressure in late systole, and thus increase PP (31,35).

## PATHOPHYSIOLOGY OF CARDIOVASCULAR EVENTS

A generally accepted mechanistic view is that an increase in arterial stiffness causes a premature return of reflected waves in late systole, increasing central pulse pressure and thus systolic BP, and damages target organs (36). Systolic BP increases the load on the left ventricle, increasing myocardial oxygen demand. In addition, arterial stiffness is associated with left ventricular hypertrophy (LVH) (5,31,35), a known risk factor for coronary events in normotensive and hypertensive patients. The increase in central PP and the decrease in diastolic BP may directly cause subendocardial ischemia. The measurement of aortic stiffness, which integrates the alterations of the arterial wall, may also reflect parallel lesions present at the site of the coronary arteries (6,12).

An increased arterial stiffness can increase the risk of stroke through several mechanisms, including an increase in central PP, influencing arterial remodelling at the site of both the extracranial and intracranial arteries, increasing carotid wall thickness and the development of stenosis and plaques (24) and the prevalence and severity of cerebral white matter lesions (8,38). The measurement of aortic stiffness may also reflect parallel lesions present at the site of cerebral vasculature. Thus, it is not surprising that aortic stiffness is able to predict not only incident stroke (19) but also the functional outcome after stroke

independent of classical risk factors (15). Another explanation is given by the differential input impedance in the brain compared with other systemic vascular beds (35). Finally, coronary heart disease and heart failure, which are favoured by high PP and arterial stiffness, are also risk factors for stroke (6,30).

## CLINICAL MEASUREMENTS OF ARTERIAL STIFFNESS AND WAVE REFLECTIONS

Arterial stiffness can be evaluated at the systemic, regional and local levels. In contrast to systemic arterial stiffness, which can only be estimated from models of the circulation, regional and local arterial stiffness can be measured directly and noninvasively at various sites along the arterial tree. A major advantage of the regional and local evaluations of arterial stiffness is that they are based on direct measurements of parameters strongly linked to wall stiffness. Reviews have been published on methodological aspects (20,25). Table 31.1 gives the main features of the various methods currently available, their respective advantages, and their theoretical, technical and practical limitations (25).

## REGIONAL MEASUREMENTS OF ARTERIAL STIFFNESS

The aorta is a major vessel of interest when determining regional arterial stiffness for at least two reasons: the thoracic and abdominal aorta makes the largest contribution to the arterial buffering function (31,35), and aortic pulse wave velocity (PWV) is an independent predictor of outcome in a variety of populations (11,18,27,28,30). However, all arterial sites have potential interest. Indeed, the forearm circulation is where blood pressure is commonly measured, and the lower limb arteries are specifically altered by atherosclerosis. Measurement of local carotid stiffness may also provide important prognostic information, since the carotid artery is a frequent site of atheroma formation.

## TWO-SITE PULSE WAVE VELOCITY MEASUREMENTS

The measurement of PWV is generally accepted as the most simple, noninvasive, robust and reproducible method with which to determine arterial stiffness. Carotid-femoral PWV is a direct measurement, and it corresponds to the widely accepted propagative model of the arterial system (30,35). Measured along the aortic and aortoiliac pathway, it is the most clinically relevant, since the aorta and its first branches are what the left ventricle 'sees', and is thus responsible for most of the pathophysiological effects of arterial stiffness. Carotid-femoral PWV has been used in epidemiological studies demonstrating the predictive value of aortic stiffness for CV events.

PWV is the speed of wave travel ( $C_0$ ) and intrinsically represents arterial stiffness, according to the Bramwell-Hill formula:  $C_0 = \sqrt{(V \cdot dP / \rho \cdot dV)}$ , where  $dV$  is the change in arterial volume ( $V$ ),  $dP$  is the change in pressure driving the change in volume, and  $\rho$  is the density of fluid. Aortic PWV is usually measured using the foot-to-foot velocity method from various waveforms (1). These are

usually obtained transcutaneously at the right common carotid artery and the right femoral artery (i.e. 'carotid-femoral' PWV), and the time delay ( $\Delta t$ , or transit time) is measured between the feet of the two waveforms (1,30,35) (Figure 31.1). The 'foot' of the wave is defined at the end of diastole, when the steep rise of the wave front begins. The transit time is the time of travel of the 'foot' of the wave over a known distance.

A variety of different waveforms can be used including pressure (1,6,18), distension (3) and Doppler (11). The distance ( $D$ ) covered by the waves is usually assimilated to the surface distance between the two recording sites, i.e. the common carotid artery (CCA) and the common femoral artery (CFA). The direct distance ( $DD$ ) is (CFA to CCA). PWV is calculated as  $PWV = D \text{ (meters)} / \Delta t \text{ (seconds)}$ . However, since the descending thoracic aorta is reached by the pressure wave at the time another pressure wave, originating from the same cardiac contraction, arrives at the carotid site, it has been recommended in a recent consensus paper (41) to measure the direct distance and apply a 0.8 coefficient to take into account the shorter pathway of the pressure.

Multiple devices using pressure waveforms recorded simultaneously are validated to provide automated measurement of PWV (25). Pressure waves can also be recorded successively from different sites, and transit time determined from the R wave of the ECG. In order to increase ease and acceptability, automatic cuff-based methods have been developed. Brachial-ankle PWV (baPWV) is calculated from travelled distance and transit time, as described previously. The measurement of baPWV includes a much longer trajectory of the pressure wave along the muscular arteries of the upper and lower limbs than along the aortic pathway, and thus may not reflect the true ageing of the aorta. However, the main assumption of the baPWV method, as well as other two-site methods, is that the transit times of the pressure waves in the upper and lower limbs were comparable, and the impact of upper and lower limb pathways on aortic stiffness measurement is limited (22). Thus, the net transit time that is measured reflects mainly the aortic pulse transit time. Using a similar cuff-based methodology for detecting the pressure waveforms and an ECG recording, a cardio-ankle PWV can be calculated. The transit time can also be measured between two flow pulses simultaneously recorded by continuous Doppler probes (11) or again sequentially with ECG gating. The finger-toe PWV method is based on similar assumptions as brachial-ankle devices (32).

## SINGLE-SITE PULSE WAVE VELOCITY MEASUREMENTS

An increasing number of methods calculate PWV over a given arterial pathway from the analysis of the brachial pressure wave. Brachial pressure wave is determined with a brachial cuff. PWV is thus referred to as 'single-site' or 'brachial cuff'-derived PWV, and apparatus as 'brachial cuff'-based devices. As detailed later, PWV is *estimated* from various parameters that are either measured or *estimated*, but PWV is not *directly* measured between two arterial sites.

Ambulatory measurement of BP and continuous monitoring of ECG over 24 hours can be used to calculate the QKD interval (25). The Arteriograph® system estimates PWV from a single-site brachial-cuff oscillometric determination of the suprasystolic waveform at the brachial

**Table 31.1** Devices and methods used for determining regional, local and systemic arterial stiffness

| Year of first publication | Device                | Method                 | Measurement site           | Predictive value for CV events (year first publication) | Ease of clinical utility | Approval by FDA |
|---------------------------|-----------------------|------------------------|----------------------------|---------------------------------------------------------|--------------------------|-----------------|
| <i>Regional Stiffness</i> |                       |                        |                            |                                                         |                          |                 |
| 1984 <sup>a</sup>         | Complior®             | Mechanotransducer      | Aorta, cf PWV <sup>b</sup> | Yes (1999)                                              | ++                       | No              |
| 1990 <sup>a</sup>         | SphygmoCor®           | Tonometer              | Aorta, cf PWV <sup>b</sup> | Yes (2011)                                              | ++                       | Yes             |
| 1991                      | WallTrack®            | Echotracking           | Aorta, cf PWV <sup>b</sup> | No                                                      | +                        | ?               |
| 1994                      | QKD                   | ECG +                  | Aorta, cf PWV <sup>b</sup> | Yes (2005)                                              | ++                       | Yes             |
| 1997 <sup>a</sup>         | Cardiovasc. Eng. Inc® | Tonometer              | Aorta, cf PWV <sup>b</sup> | Yes (2010)                                              | +                        | NA              |
| 2002                      | ArtLab®               | Echotracking           | Aorta, cf PWV <sup>b</sup> | No                                                      | ++                       | Yes             |
| 2002                      | Ultrasound systems    | Doppler probes         | Aorta, cf PWV <sup>b</sup> | Yes (2002)                                              | +                        | NA              |
| 2002                      | Omron VP-1000®        | Pressure cuffs         | Aorta, ba PWV <sup>b</sup> | Yes (2005)                                              | +++                      | Yes             |
| 2007                      | CAVI-VaSera®          | ECG + Pressure cuffs   | Aorta, ca PWV <sup>b</sup> | Yes (2014)                                              | +++                      | Yes             |
| 2008                      | Arteriograph®         | Arm pressure cuff      | Aorta, aa PWV <sup>b</sup> | Yes (2013)                                              | ++                       | No              |
| 2009                      | MRI, ArtFun®          | MRI                    | Aorta, aa PWV <sup>b</sup> | Yes (2014)                                              | +                        | NA              |
| 2010                      | Mobil-O-Graph®        | Arm pressure cuff      | Aorta, cf PWV <sup>c</sup> | No                                                      | ++                       | Yes             |
| 2010                      | Ultrafast®            | Echography             | Common carotid             | No                                                      | –                        | No              |
| 2013                      | pOpmetre®             | Photoplethysmography   | Aorta, ft PWV <sup>b</sup> | No                                                      | +++                      | No              |
| 2017                      | Withings®             | Ballistocardiography   | Aorta                      | No                                                      | +++                      | ?               |
| <i>Local stiffness</i>    |                       |                        |                            |                                                         |                          |                 |
| 1991                      | WallTrack®            | Echotracking           | CCA <sup>d</sup> , CFA, BA | No                                                      | +                        | No              |
| 1992                      | NIUS®                 | Echotracking           | RA                         | No                                                      | +/-                      | No              |
| 2002                      | ArtLab®, MyLab®       | Echotracking           | CCA <sup>d</sup> , CFA, BA | Yes (2014)                                              | ++                       | Yes             |
|                           | Ultrasound systems    | Echography             | CCA <sup>d</sup> , CFA, BA | No                                                      | +                        | ?               |
| 2009                      | MRI, ArtFun®          | Cine-MRI               | AA, DA                     | No                                                      | +                        | NA              |
| <i>Systemic stiffness</i> |                       |                        |                            |                                                         |                          |                 |
| 1989                      | Area method           | Diastolic decay        |                            | No                                                      | +/-                      | NA              |
| 1995                      | HDI PW CR-2000®       | Modif. Windkessel      |                            | No                                                      | +                        | Yes             |
| 1997 <sup>a</sup>         | Cardiovasc. Eng. Inc® | Tonometer/Doppler/Echo |                            | Yes (2010)                                              | +/-                      | NA              |
| 2009                      | MRI, ArtFun®          | Cine-MRI               | AA, DA                     | No                                                      | +                        | NA              |

Source: Adapted from Laurent S et al. *Can J Cardiol* 2016; 32: 669–679, with permission.

<sup>a</sup> Apparatus used in pioneering epidemiological studies showing the predictive value of aortic stiffness for CV events.

<sup>b</sup> cf, carotid-femoral; ba, brachial-ankle; ca, cardiac-ankle; aa, aortic arch; ft, finger-toe; PWV, pulse wave velocity.

<sup>c</sup> Estimated, not measured.

<sup>d</sup> All superficial arteries, including particularly those mentioned; Ao, aorta; CCA, common carotid artery; CFA, common femoral artery; BA, brachial artery; RA, radial artery; AA, ascending aorta; DA, descending aorta. FDA means agreement by FDA for the market, which is necessary for use in routine clinical practice, but is not necessary for use in research centres. NA means not applicable. All apparatus have CE agreement by the European Community.

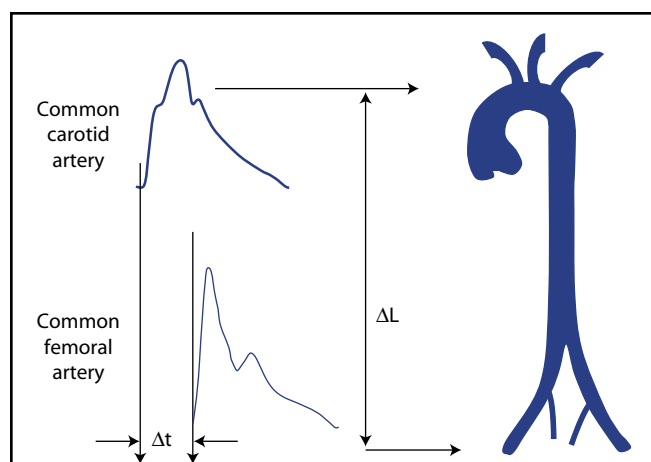


**Figure 31.1** Measurement of carotid-femoral pulse wave velocity with the foot-to-foot method. The waveforms are usually obtained transcutaneously at the right common carotid artery and the right femoral artery. The time delay ( $\Delta t$ , or transit time) is measured between the feet of the two waveforms. The distance ( $\Delta L$ ) covered by the waves is usually assimilated to the surface distance between the two recording sites, i.e. the common carotid artery and the common femoral artery. PWV is calculated as  $PWV = 0.8 \times \Delta L \text{ (meters)} / \Delta t \text{ (seconds)}$ . (From Laurent S et al. *Eur Heart J* 2006; 27: 2588–605, with permission.)

artery site (25). The Mobil-O-Graph® system takes advantage of oscillometric recording of brachial artery pressure waveform to synthesize the central pulse wave by applying a transfer function (25). Eventually, aortic pulse wave velocity can be reliably measured with a bathroom scale combining the principles of ballistocardiography and impedance plethysmography on a single foot (9).

### LOCAL DETERMINATION OF ARTERIAL STIFFNESS

Local arterial stiffness of superficial arteries can be directly determined using high-resolution echotracking devices (3,4,14,42). Carotid stiffness may be of particular interest, since artery atherosclerosis is frequent. The advantage of high-resolution echotracking devices is their high precision for determining diameter at diastole and stroke changes in diameter, compared with classical video-image analysis. Magnetic resonance imaging (MRI) is increasingly popular since it allows combined determination of cardiac and aortic structure and function (25). However, most pathophysiological and pharmacological studies have used echotracking techniques.

### SYSTEMIC ARTERIAL STIFFNESS

A methodology based on an electrical circuit, based on a modified Windkessel model, has been developed to determine a proximal capacitive compliance and a distal oscillatory compliance (10). Systemic arterial compliance can also be determined using the 'area method' which

requires measurement of aortic blood flow (velocimeter at the suprasternal notch) and associated driving pressure by applanation tonometry over the proximal right common carotid artery. A number of theoretical, technical and practical limitations impair their widespread application in the clinical setting (25).

## CLINICAL IMPORTANCE

### ARTERIAL DAMAGE IN HYPERTENSION AND ASSOCIATED CLINICAL CONDITIONS

A large number of publications and several reviews (20,35,37) have reported the various pathophysiological conditions associated with increased arterial stiffness and wave reflections. Apart from the dominant effect of blood pressure and ageing, they include (a) physiological conditions (42), such as low birth weight, menopausal status, and lack of physical activity; (b) the genetic background such as a parental history of hypertension, diabetes or myocardial infarction, and genetic polymorphisms; (c) CV risk factors such as obesity, smoking, hypertension, hypercholesterolemia, impaired glucose tolerance, metabolic syndrome (37), type 1 and 2 diabetes, hyperhomocysteinemia and high CRP level; (d) CV diseases such as coronary heart disease, congestive heart failure and fatal stroke; and (e) primarily non-CV diseases, such as end-stage renal disease (ESRD) and moderate chronic kidney disease, and chronic low-grade inflammation diseases such as rheumatoid arthritis, systemic vasculitis, systemic lupus erythematosus and inflammatory bowel disease (45).

### PREDICTIVE VALUE OF ARTERIAL STIFFNESS AND WAVE REFLECTION

A major reason for measuring arterial stiffness and wave reflections 'routinely' in clinical practice in hypertensive patients comes from the repeated demonstration that arterial stiffness has an independent predictive value for CV events (2,6,11,15,18,19,27,28,30,43).

### ARTERIAL STIFFNESS AS INTERMEDIATE ENDPOINT

Several longitudinal epidemiological studies have demonstrated the predictive value of arterial stiffness for CV events. The largest amount of evidence has been given for aortic stiffness, measured through carotid-femoral PWV. Aortic stiffness has independent predictive value for all-cause and CV mortality, fatal and nonfatal coronary events, and fatal strokes not only in patients with uncomplicated essential hypertension (5,18,19) but also in patients with type 2 diabetes (11) or ESRD (3), in elderly subjects (28) and in the general population (27,30). Two meta-analyses (2,43) consistently showed the independent predictive value of aortic stiffness for fatal and nonfatal CV events in various populations.

The independent predictive value of aortic stiffness has been demonstrated after adjustment to classical cardiovascular risk factors, including brachial pulse pressure. This indicates that aortic stiffness has a better predictive value than each of the classical risk factors. In addition, aortic



stiffness retains its predictive value for CHD events after adjustment to the Framingham Risk Score, suggesting that aortic stiffness has an added value to a combination of CV risk factors (5). One reason may be that aortic stiffness integrates the damage of CV risk factors on the aortic wall over a long period of time, whereas BP, glycemia and lipids can fluctuate over time, and their values, recorded at the time of risk assessment, may not reflect the true values damaging the arterial wall (21). Another explanation may be that arterial stiffness is able to detect patients in which arterial risk factors are translated into real risk. Aortic stiffness can thus be considered as an intermediate endpoint for CV events (21).

### ARTERIAL STIFFNESS AS SURROGATE ENDPOINT

A surrogate endpoint is a biomarker that is intended as a substitute for a clinical endpoint. In order to be considered as a surrogate endpoint of cardiovascular events, a biomarker should satisfy several criteria, such as proof of concept, prospective validation, incremental value, clinical utility, clinical outcomes, cost-effectiveness, ease of use, methodological consensus and reference values (16,21). The repeated demonstration of the predictive value of arterial stiffness for CV events lead to its inclusion in the 2013 European Society of Hypertension (ESH) Guidelines for the Management of Arterial Hypertension (26), as target-organ damage. A position paper from the European Society of Cardiology (ESC) working group on peripheral circulation (44) scrutinized the role of peripheral (i.e. not related to coronary circulation) noninvasive vascular biomarkers for primary and secondary cardiovascular disease prevention. Carotid-femoral PWV was retained as one of the few biomarkers that fulfilled most of the criteria and therefore was close to being considered a clinical surrogate endpoint (44). Finally, a recent call to action of the Lancet Commission on Hypertension (33) addressed the global burden of raised blood pressure through a life-course strategy based on the quantification of early vascular ageing, an equivalent of arterial stiffness.

### THRESHOLD VALUE OF AORTIC STIFFNESS AND REFERENCE VALUES

Although the relationship between aortic stiffness and events is continuous, a threshold of 10 m/sec has been suggested as a conservative estimate of significant alterations of aortic function in middle-age hypertensives (41) and included in the 2013 ESH Guidelines for the Management of Arterial Hypertension (26). High aortic PWV thus represents target-organ damage, which needs to be detected during estimation of CV risk in hypertensives. Reference values for PWV (34) have been established in 1455 healthy subjects and a larger population of 11,092 subjects with CV risk factors (Table 31.2).

### PREDICTIVE VALUE OF CAROTID STIFFNESS

The predictive value of carotid stiffness, locally measured with high-resolution echotracking at the carotid site, has been reported in various populations. Carotid stiffness was predictive of CV events in a small number of patients with ESRD (3) or following renal transplantation. Ten studies totalizing 22,472 individuals were included in a recent aggregate data meta-analysis showing that carotid stiffness was associated with incident stroke independent of CV

**Table 31.2** Distribution of carotid-femoral pulse wave velocity (cfPWV, m/s) according to the age category in the normal values population (1455 subjects)

| Age category (years) | Mean ( $\pm$ 2SD) | Median (10-90 pc) |
|----------------------|-------------------|-------------------|
| <30                  | 6.2 (4.7-7.6)     | 6.1 (5.3-7.1)     |
| 30-39                | 6.5 (3.8-9.2)     | 6.4 (5.2-8.0)     |
| 40-49                | 7.2 (4.6-9.8)     | 6.9 (5.9-8.6)     |
| 50-59                | 8.3 (4.5-12.1)    | 8.1 (6.3-10.0)    |
| 60-69                | 10.3 (5.5-15.0)   | 9.7 (7.9-13.1)    |
| $\geq$ 70            | 10.9 (5.5-16.3)   | 10.6 (8.0-14.6)   |

Source: *Eur Heart J* 2010; 31: 2338-2350, with permission.

Abbreviations: SD, standard deviation; pc, percentile.

factors and aortic stiffness (42). In addition, carotid stiffness improved stroke risk prediction beyond Framingham and aortic stiffness (42).

### PHARMACOLOGY OF ARTERIAL STIFFNESS AND WAVE REFLECTION

A large number of publications and several reviews (7,20,23,29,39,40) reported the changes in arterial stiffness and wave reflections after various interventions, either non-pharmacologic or pharmacologic. Non-pharmacological treatments that are able to reduce arterial stiffness include (20) exercise training, dietary changes (including weight loss, low-salt diet, moderate alcohol consumption, garlic powder, alpha-linoleic acid and fish oil), and hormone-replacement therapy (HRT).

Pharmacological treatments which are able to reduce arterial stiffness include (7,20) (a) antihypertensive treatment, such as diuretics in the elderly, beta-blockers, ACE inhibitors (29,40), AT1 blockers (23), and calcium channel antagonists (39); (b) treatments of congestive heart failure, such as ACE inhibitors, nitrates and aldosterone antagonists; (c) hypolipidemic agents such as statins; (d) antidiabetic agents such as thiazolidinediones; and (e) advanced glycation end-product (AGE)-breakers, such as alagebrium (ALT-711). Whether the reduction in arterial stiffness after antihypertensive treatment is only due to BP lowering or if additional BP-independent effects are involved is still debated. To our knowledge, some studies unequivocally showed that antihypertensive treatment was able to reduce arterial stiffness and/or wave reflections independent of the reduction in brachial BP, for instance either acutely after a calcium channel blocker (39) or after long-term ACE inhibition (29,40) or angiotensin-receptor blockade (23).

### CONCLUSION

This chapter highlights the importance of arterial stiffness, not only for assessing CV risk, but also for predicting CV outcomes. Arterial stiffening also provides direct evidence of target-organ damage, which is of major importance in determining the overall CV risk of the hypertensive

patient. Indeed, measurement of arterial stiffness may avoid patients being mistakenly classified as being at low or moderate risk, when they actually have an abnormally high arterial stiffness or central PP placing them within a higher risk group.

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## REFERENCES

- Asmar R, Benetos A, Topouchian J et al. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension* 1995; 26: 485–490.
- Ben-Shlomo Y, Spears M, Boustred C et al. Aortic pulse wave velocity improves cardiovascular event prediction: An individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol* 2014; 63: 636–646.
- Blacher J, Pannier B, Guerin A et al. Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end-stage renal disease. *Hypertension* 1998; 32: 570–574.
- Bossuyt J, Engelen L, Ferreira I et al. Reference intervals for local arterial stiffness. Part B: Femoral artery. *J Hypertens* 2015; 33: 1997–2009.
- Boutouyrie P, Laurent S, Girerd X et al. Common carotid artery distensibility and patterns of left ventricular hypertrophy in hypertensive patients. *Hypertension* 1995; 25(Part 1): 651–659.
- Boutouyrie P, Tropeano AI, Asmar R et al. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: A longitudinal study. *Hypertension* 2002; 39: 10–15.
- Boutouyrie P, Lacolley P, Briet M et al. Pharmacological modulation of arterial stiffness. *Drugs* 2011; 71: 1689–1701.
- Briset M, Boutouyrie P, Pico F et al. Large vessel correlates of cerebral small vessel disease. *Neurology* 2013; 80: 1–8.
- Campo D, Khettab H, Yu R et al. Measurement of aortic pulse wave velocity with a connected bathroom scale. *Am J Hypertens* 2017; 30: 876–883.
- Cohn JN, Finkelstein S, McVeigh G et al. Noninvasive pulse wave analysis for the early detection of vascular disease. *Hypertension* 1995; 26: 503–508.
- Cruickshank K, Riste L, Anderson SG et al. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: An integrated index of vascular function? *Circulation* 2002; 106: 2085–2090.
- Dart AM, Gatzka CD, Kingwell BA et al. Brachial blood pressure but not carotid arterial waveforms predict cardiovascular events in elderly female hypertensives. *Hypertension* 2006; 47: 785–790.
- Dobrin P. Vascular Mechanics. In: Shepherd JT, Abboud FM (eds). *Handbook of Physiology. Section 2: The Cardiovascular System. Volume III: Peripheral Circulation and Organ Blood Flow*. American Physiology Society, Baltimore, MD; 1983: 65–102.
- Engelen L, Bossuyt J, Ferreira I et al. Reference values for local arterial stiffness. Part A: Carotid artery. *J Hypertens* 2015; 33: 1881–1896.
- Gasecki D, Rokek A, Kwarciany M et al. Pulse wave velocity predicts functional outcome in patients after ischemic stroke. *Stroke* 2012; 43: 543–544.
- Hlatky MA, Greenland P, Arnett DK et al. Criteria for evaluation of novel markers of cardiovascular risk: A scientific statement from the American Heart Association. *Circulation* 2009; 119: 2408–2416.
- Lacolley P, Regnault V, Segers P, Laurent S. Vascular smooth muscle cell and arterial stiffening: Relevance in development, ageing and disease. *Phys Rev* 2017; 97: 1555–1617.
- Laurent S, Boutouyrie P, Asmar R et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; 37: 1236–1241.
- Laurent S, Katsahian S, Fassot C et al. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. *Stroke* 2003; 34: 1203–1206.
- Laurent S, Cockcroft J, Van Bortel L et al. Expert Consensus Document on arterial stiffness: Methodological aspects and clinical applications. *Eur Heart J* 2006; 27: 2588–2605.
- Laurent S, Briet M, Boutouyrie P. Arterial stiffness and central pulse pressure as surrogate markers: Needed clinical trials. *Hypertension* 2012; 60: 518–522.
- Laurent S, Mousseaux E, Boutouyrie P. Arterial stiffness as an imaging biomarker: Are all pathways equal? *Hypertension* 2013; 62: 10–12.
- Laurent S, Boutouyrie P. On behalf of the Mechanism Vascular Study Investigators. Dose-dependent inward arterial remodeling and destiffening after olmesartan in hypertensive with metabolic syndrome. *Hypertension* 2014; 64: 709–716.
- Laurent S, Boutouyrie P. The structural factor in hypertension: Large and small artery alterations. *Circ Res* 2015; 116: 1007–1021.
- Laurent S, Marais L, Boutouyrie P. The non-invasive assessment of vascular aging. *Can J Cardiol* 2016; 32: 669–679.
- Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; 34: 2159–2219.
- Mattace-Raso FU, van der Cammen TJ, Hofman A et al. Arterial stiffness and risk of coronary heart disease and stroke: The Rotterdam Study. *Circulation* 2006; 113: 657–663.
- Meaume S, Benetos A, Henry OF et al. Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. *Arterioscler Thromb Vasc Biol* 2001; 21: 2046–2050.
- Mitchell GF, Izzo Jr JL, Lacourcière Y et al. Omapatrilat reduces pulse pressure and proximal aortic stiffness in patients with systolic hypertension: Results of the conduit hemodynamics of Omapatrilat International Research Study. *Circulation* 2002; 105: 2955–2961.
- Mitchell GF, Hwang SJ, Vasan RD et al. Arterial stiffness and cardiovascular events. The Framingham Heart Study. *Circulation* 2010; 121: 505–511.
- Nichols WW, O'Rourke MF. *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*. 5th ed. Oxford University Press; 2005: 624 pages.
- Obeid H, Khettab H, Marais L et al. Evaluation of arterial stiffness by finger-toe pulse wave velocity: Influence and validation of timing algorithm and signal procession chain. *J Hypertens* 2017; 35: 1618–1625.
- Olsen M, Angell S, Asma S et al. A call to action and a life-course strategy to address the global burden of raised blood pressure on current and future generations. The Lancet Commission on Hypertension. *Lancet* 2016; 388: 2665–2712.
- Mattace Raso F, Hofman A, Verwoert GC. Reference Values for Carotid-Femoral Pulse Wave Velocity in the Reference Values for Arterial Stiffness' Collaboration Database. *Eur Heart J* 2010; 31: 2338–2350.
- Safar ME, O'Rourke MF. *Handbook of Hypertension. Volume 23: Arterial Stiffness in Hypertension*. Elsevier; 2006: 598 pages.
- Safar ME, Nilsson PM, Blacher J, Mimran A. Pulse pressure, arterial stiffness, and end-organ damage. *Curr Hypertens Rep* 2012; 14: 339–344.
- Safar ME, Balkau B, Lange C et al. Hypertension and vascular dynamics in men and women with metabolic syndrome. *J Am Coll Cardiol* 2013; 61: 12–19.
- Scuteri A, Nilsson P, Tsourio C et al. Microvascular brain damage: Pathophysiological consideration and clinical implications. *J Hypertens* 2011; 29: 1469–1477.
- Stefanadis C, Dornellis J, Vlachopoulos C et al. Aortic function in arterial hypertension determined by pressure-diameter relation: Effects of diltiazem. *Circulation* 1997; 96: 1853–1858.
- Tropeano AI, Boutouyrie P, Pannier B et al. Brachial pressure-independent reduction in carotid stiffness after long-term angiotensin-converting enzyme inhibition in diabetic hypertensives. *Hypertension* 2006; 48: 80–86.
- Bortel LMV, Laurent S, Boutouyrie P et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens* 2012; 30: 445–448.
- Sloten TTV, Sedaghat S, Laurent S et al. Carotid stiffness is associated with incident stroke: A systematic review and meta-analysis. *J Am Coll Cardiol* 2015; 66: 2116–2125.
- Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: A systematic review and meta-analysis. *J Am Coll Cardiol* 2010; 55: 1318–1327.
- Vlachopoulos C, Xaplanteris P, Aboyans V et al. The role of vascular biomarkers for primary and secondary prevention. A position statement from the European Society of Cardiology working group on peripheral circulation. *Atherosclerosis* 2015; 241: 507–532.
- Zanoli L, Rastelli S, Granata A et al. Arterial stiffness in inflammatory bowel disease: A systematic review and meta-analysis. *J Hypertens* 2016; 34: 822–829.

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## INTRODUCTION

Hypertension, obesity and diabetes often coexist, and this constellation is known as the metabolic syndrome. It has been proposed that this phenotype is more than a coincidence, and that microvascular damage may well be one of the initial pathophysiological stages in the development of diabetes as well as hypertension. A better knowledge of the workings of microcirculation undoubtedly will lead to the development of novel therapies to treat the metabolic syndrome.

Vascular smooth muscle cells (VSMCs) are responsible for managing much of the peripheral systemic blood flow and contribute to what we measure as the clinic blood pressure. Vascular tone is controlled by factors secreted by endothelial cells, sympathetic nerves and circulating hormones. In small resistance arteries that determine peripheral vascular resistance ( $<300\ \mu\text{m}$  relaxed internal diameter), a degree of contractile response to pressure is observed that is independent of neurohormonal stimuli and the endothelium. This is known as myogenic tone (1). The contractile apparatus of VSMC is made up of three components (2,3): thin actin filaments; intermediate filaments or cytoskeleton of the cell, which couples actin and myosin with the cell membrane to offer a support mechanism to prevent overextension and excessive shortening; and thick myosin filaments. The VSMCs in resistance arteries and arterioles have a membrane potential of  $-60$  to  $-75\ \text{mV}$  in vitro, and  $-40$  to  $-55\ \text{mV}$  in vivo. The calcium channels on VSMC cell membrane exist as either conducting or nonconducting in conformation. Cell depolarisation leads to an increase in the open-state probability of the calcium channels, the probability that the  $\text{Ca}^{2+}$  channels are open (Popen), and hyperpolarisation decreases  $\text{Ca}^{2+}$  entry by reducing the Popen, resulting in the closure of calcium channels (4,5).

Calcium plays a pivotal role in VSMC contraction. The process can be initiated by a variety of pathways that lead to an eventual increase in intracellular calcium concentration. Four molecules of  $\text{Ca}^{2+}$  bind to the intracellular protein calmodulin (CaM) and activate it. Activated calmodulin  $[(\text{Ca}^{2+})_4\text{CaM}]$  then activates myosin light-chain kinase (MLCK), which leads to phosphorylation of

myosin light chains, enabling its interaction with actin and initiation of contraction (3,6). A reduction in intracellular  $\text{Ca}^{2+}$  concentration leads to dephosphorylation of the myosin light chain via myosin phosphatase, resulting in relaxation (6). Hyperpolarisation of VSMCs leads to relaxation, leading to decreased vascular tone and resulting in an increase in the vessel diameter. Hyperpolarisation of VSMCs is brought about via two pathways: first, endothelium-derived hyperpolarising factor (EDHF), and second, EDHF-mediated responses involving  $\text{K}^+$  channels. The VSMC relaxation observed independent of nitric oxide (NO) and prostacyclin (in the presence of their inhibitors) was initially thought to result from an EDHF. Further research has shown that a number of factors lead to hyperpolarisation of the VSMC including NO, hydrogen sulphide, reactive oxygen species and metabolites of arachidonic acid (7,8).

In addition, endothelial cells (ECs) play a crucial role. They express receptors for a variety of factors including acetylcholine, catecholamines, angiotensin and serotonin, and are responsible for producing a variety of factors including endothelium-derived relaxing factors (EDRFs) and endothelium-derived constricting factors (EDCFs). The endothelium is also involved in immune responses, haemostasis, regulation of growth and production of extracellular matrix components (9–12). The endothelium functions as a sensor, reacting to the various factors in the bloodstream via its surface receptors and by reacting directly to the hemodynamic forces produced by blood flowing through the vessel. Once the message to change vascular tone is 'sensed', the endothelium 'transmits' it to the vascular smooth muscle cells via EDRFs or EDCFs. The principal EDRFs have been identified as NO (13,14) and prostacyclin (15). EDHF-mediated responses are endothelium-dependent relaxations that are independent of all these mediators and are associated with hyperpolarisation of both the ECs and the VSMCs. These responses involve the activation of endothelial calcium-activated potassium (Kca) channels: large (BKca) (expressed in all VSMCs, very poorly expressed in ECs), intermediate (IKca) (expressed in ECs) and small (SKca) (expressed in ECs).

One explanation suggests that once the endothelium has received the appropriate signal required for vasodilatation,



there is an increase in its  $[Ca^{2+}]_i$  leading to opening of  $IK_{Ca}$  and  $SK_{Ca}$  channels, resulting in efflux of  $K^+$  and its accumulation in the myoendothelial junction. This process leaves the endothelial cell hyperpolarised. Then VSMCs become hyperpolarised by either (a) transmission of the hyperpolarisation from EC to VSMC via gap junctions, or (b) induction of hyperpolarisation in VSMC by the  $K^+$  released from the EC into the myoendothelial junction. The  $K^+$  is thought to activate  $Na^+-K^+-ATPase$  on VSMC (5,7,8).

This partly explains how circulating factors can affect vessel tone by stimulating ECs and leading to changes in VSMC tone. Also, there is growing evidence that control of microvessel tone is not purely an 'inside-out' phenomenon and reliant on circulating factors, but there is an element of 'outside-in' influence from the perivascular adipose tissue beyond what can be expected of sympathetic nerve control of arteries.

The changes observed in hypertension involve both vascular and cardiac remodelling. An early cross-sectional study of mild hypertension reported that the predominant hemodynamic feature was a high cardiac output (16), and this observation has been confirmed consistently since. Although not invariably so, the high cardiac output is accompanied by an increased heart rate, and several studies have demonstrated that when oxygen consumption is measured, both cardiac output and this parameter are raised (17). In the mild early stages of essential hypertension, the peripheral resistance is low, although the crucial point is that it remains inappropriately high for the corresponding cardiac output. A 20-year longitudinal study of the hemodynamic of essential hypertension confirmed the finding of initially increased cardiac index, heart rate, oxygen consumption and blood pressure with normal peripheral resistance (18). However, over this period the high cardiac index and normal total peripheral resistance pattern changes to a low cardiac index and high resistance pattern. Again, the inappropriately high level of vascular resistance for the increase in cardiac output is a hallmark of early hypertension. Such a hemodynamic profile could be ascribed to a high sympathetic nervous tone with the resulting increased drive to the heart, peripheral circulation and metabolic receptors, which would then promote enhanced oxygen consumption. Other studies demonstrated that autonomic blockade of the heart in mild hypertensive patients restored cardiac output to normal, and there was a combination of increased sympathetic tone and decreased parasympathetic activity in such individuals (19,20). This combination of increased sympathetic discharge coupled with a reduced parasympathetic activity suggests that the abnormality in essential hypertension is one of integrated function in the medulla oblongata.

Recent data have proposed that the autonomic changes in hypertension may be a consequence of neurovascular compression on the left ventrolateral medulla. Therefore, it should follow that the resulting increased sympathetic activity would be distributed to all innervated organs and vascular beds, producing uniform vasoconstriction and the predicted cardiac indices. There is evidence for this in the heart, kidney and skeletal muscle but it has not been confirmed in studies of the hepatomesenteric circulation (21). In other words, it is difficult to provide evidence for a ubiquitous abnormality of sympathetic function in all vascular beds, although the overall integrated hemodynamic profile can be ascribed to increased sympathetic discharge.

## STRUCTURAL CHANGES IN THE CIRCULATION

Since the work of Bright and Johnson, it has been recognised that the walls of medium-sized arteries are thickened in hypertension. However, it has to be conceded that their contribution to vascular resistance is small. The histopathological change appears to be hypertrophy, and indeed the heart and medium-sized blood vessels demonstrate this hypertrophic response to blood pressure. In addition, until the heart dilates it is of interest to note that the hypertrophic response takes place at the expense of the ventricular cavity: in other words, there is inward encroachment on the chamber space. Therefore, in any form of sustained hypertension there is an alteration in the architecture of the circulation that inevitably occurs in consequence. At the level of the resistance artery where the internal diameter of the blood vessels is around 250  $\mu m$  or less, there is evidence of a reduced lumen diameter and increased media thickness: lumen diameter ratio. This was originally reported in necropsy specimens (22) and subsequently confirmed in segments of artery mounted as isometric ring preparations on wires and in vessels perfused in vitro (23). Detailed histological analyses more recently carried out have suggested that eutrophic inward remodelling occurs at this point in the circulation. By this it is meant that there is a narrowing of the vascular lumen without having to invoke a growth response of the arterial wall (24). A small amount of hypertrophy may be observed in some pathological states where hypertrophy may supervene and is an adverse prognostic sign (25).

The most compelling issue is whether structural changes in these small blood vessels occur before blood pressure rises or in consequence of the hypertension. The corollary of what has been described previously namely the existence of excessive sympathetic nervous activity in the early stages of the development of hypertension being the trigger for the majority of this disorder, has made it tempting to regard the small artery as changing shape in consequence. In a study of small artery structural characteristics in first-degree offspring of hypertensive patients in whom one would predict an increasing propensity to developing hypertension, there was no evidence of any alteration despite mean blood pressures having been higher (26). Also, in another study in young genetically hypertension-prone spontaneously hypertensive rats (SHRs) where non-constricting ligatures were placed on the iliac artery and the animals allowed to mature until a point when the ligature compressed gradually on the vessel, the pressures in the hind limb were kept low and structural changes were not observed (27). Therefore, the impression gained is that the vascular changes follow rises in pressure. However, most recently it has been reported that mice mutant for *EMILIN-1*, a cysteine-rich secreted glycoprotein expressed in the vascular tree, display hypertension, increased peripheral vascular resistance and reduced blood vessel size. *EMILIN-1* inhibits  $TGF-\beta$  signalling by binding specifically to pro $TGF-\beta$  precursor and prevents its maturation by furin convertases in the extracellular space (28). Therefore, in this model at least, structural changes may precede hypertension. The area remains contentious. The other important issue to consider at this time is whether structural alterations amplify vasoconstrictor responses. Korner and Angus developed a theory with respect to the

role of an increased lumen ratio in the resistance vasculature, which maintains the elevated peripheral resistance in hypertension. This is based on calculating resistance from pressure and flow recordings and consequently calculating an arbitrary radius from the fourth route of  $1/R$  (Poiseuille's law). The calculations indicate a constant narrowing in vessel radius from maximal dilatation to maximal constriction in hypertension, which acts to amplify changes in resistance. This has been very controversial. A number of studies have consistently reported structural changes predicted and described previously in small arteries with an internal diameter between 200–300  $\mu\text{m}$  from patients with essential hypertension and in various animal models with the disease. Such reports should strengthen this amplifier theory. However, direct supporting evidence needs the measurement of the lumen diameter of blood vessels demonstrated to contribute to the control of resistance in a vascular bed but under extremely rigorous conditions (29). In this context, particular emphasis should be placed on measurement of diameter made at physiological levels of tone. This has been carried out using studies of functional and structural characteristics of small mesenteric arteries cannulated and pressurised *in vitro*. Such arteries have spontaneous myogenic tone at physiological pressures, which is a major determinant of diameter in the resistance vasculature unlike the upstream mesenteric arteries frequently studied in hypertension research. Distal mesenteric arteries were pressurised to 63% of the mean aortic pressure of each rat. It is the pressure recorded at this level of the mesenteric/intestinal vasculature in both rat strains indicating a location within the resistance vasculature. In the absence of tone, SHR vessels had a reduced lumen diameter, although this was of borderline significance. Nevertheless, a clear increase in wall lumen ratio was observed. However, with spontaneous myogenic tone, lumen diameter became identical in the two strains, and importantly remained identical as tone was increased throughout the complete noradrenaline concentration response curve (30). Such data do not support the hypothesis of an increased wall lumen ratio acting as an amplifier in hypertension. Studies in isolated segments of small arteries or in isolated intact vascular beds can provide clear insights into basic mechanisms; however, these can only be considered as hypothesis-generating regarding the relevance of a particular mechanism. Surprisingly few studies have actually been carried out to date in intact conscious animals, and overall the results are not consistent with an amplifier hypothesis. In one of these, blood pressure and total peripheral resistance responses to infusion of the alpha agonist phenylephrine at two rates at the development phase of hypertension in SHRs aged 8–26 weeks was compared with age-matched Wistar Kyoto (WKY) rats before and after ganglionic blockade. At 16 weeks of age, more complete dose-response curves to the alpha agonist methoxamine were constructed. Total peripheral resistance (TPR) responses to phenylephrine were significantly less in SHRs versus WKY rats at all ages in the study. The higher infusion rate increased mean arterial pressure by approximately 80 mmHg and nearly doubled the TPR. In contrast, blood pressure and TPR responses to methoxamine were enhanced in SHRs in low rates of infusion but did not differ at the higher rates. Assuming that methoxamine is the most specific alpha agonist, these results are suggestive for functional rather than structural changes being contributory to the hyper-responsiveness to modest

alpha receptor stimulation (31). From a pathophysiological perspective, changes in TPR in response to low/modest stimulation appear to be a relevant parameter of TPR reactivity. More marked stimulation leading to five- or six-fold increases in TPR may lead to increased responsiveness but these are unlikely to be relevant for the maintenance or development of most hypertension. In other words, *in vivo* studies do not actually support the hypothesis that structural changes amplify vasoconstrictor responses throughout the circulation.

## REMODELLING AND HYPERTROPHY IN THE CIRCULATION

To understand how hypertension produces non-hypertrophic changes in small arteries, one must look at the physiological role of the resistance vasculature. At normal pressures, these vessels exhibit a level of contraction (myogenic tone), which is independent of neurohormonal influences, and in functioning in this way the response enables arteries to constrict or dilate in response to changes in upstream pressure. This process, known as the myogenic response, is only observed in smaller resistance arteries, which mediate autoregulation of blood flow and stabilise capillary pressure. This ensures that target organs downstream are supplied with oxygenated blood at a constant flow and pressure. Hypertrophy is observed in vessels which do not possess myogenic tone, whereas in smaller resistance arteries, initial increase in pressure will bring about an increased myogenic constriction. If an individual has untreated hypertension, then there will be prolonged myogenic constriction as the resistance vasculature endeavours to protect the target organs downstream from pressure-induced damage brought about by an increase in blood flow. Prolonged vasoconstriction will lead to inward eutrophic remodelling and/or a reduced arterial distensibility. The structural difference between large-conduit and medium-sized arteries and downstream resistance vessels is apparent in many models of hypertension; for example, in a hypertensive model brought on by chronic NO synthase inhibition. In addition, the magnitude and duration of an increase in intraluminal pressure plays a role in determining the remodelling response.

## MOLECULAR MECHANISMS RESPONSE FOR EUTROPHIC REMODELLING

Eutrophic inward remodelling is a process of structural adaptation observed in most forms of hypertension, including the onset of hypertension and milder hypertensive states. However, a few animal models of hypertension, such as a model developing hypertension independent of the renin-angiotensin system (BPH-2 mice), demonstrate hypertrophy as the predominating structural change. Inward eutrophic remodelling is a relatively fast functional adaptation observed after prolonged vasoconstriction and is thought to be an energetically favoured mechanism to preserve a lumen diameter for long periods. The process is also the preferred physiological mechanism by which wall stress can be normalised while maintaining vasomotor tone. Studies of the well-characterised TGR(mREN2)27



rat, which develops fulminant hypertension from 4 weeks of age, have demonstrated that eutrophic inward remodelling occurs from 4 weeks and is dependent on the integrin  $\alpha V\beta 3$ , a multifunctional extracellular matrix (ECM) receptor (32). However, hypertrophy does begin to appear between 6 and 8 weeks of age. This is important and is discussed later. The ECM of resistance arteries is subject to tensile force exerted by blood pressure, which is transferred through integrins across the cell membrane and linked by molecular complexes to the cytoskeleton. Specific integrin subtypes are utilised initially for the mechanotransduction of pressure. Using peptides and specific antibodies, it has been shown that integrins  $\alpha V\beta 3$  and  $\alpha 5\beta 1$  indirectly regulate the myogenic response by influencing the control of calcium flow through ion channels;  $\alpha 5\beta 1$  is responsible for the initial calcium influx required to establish vascular tone, and  $\alpha V\beta 3$  mediates force maintenance by calcium sensitisation of contractile components. These integrins can form complexes which regulate cytoskeletal dynamics and maintain a vascular myogenic force at a given pressure (33). This is ameliorated if there is cytoskeletal disruption. Cytoskeletal proteins such as heat-shock protein 27 (HSP27) activated by RhoA kinases have been shown to regulate myogenic tone. It is now clear that RhoA signalling plays a central role in both calcium sensitisation and regulation of actin dynamics in small artery remodelling. In contrast to molecular signalling mechanisms behind the vascular myogenic response, relatively few data are available on the role of integrins and the underlying biochemical pathways of the next stage of vascular adaptation for hypertension, which is the migration of vascular smooth muscle cells towards a narrow lumen. Remodelling involves a migratory process following prolonged vasoconstriction whereby existing vascular smooth cells reposition themselves in the vascular wall and thereby produce a narrow lumen. A characteristic of migrating cells *in vitro* is the presence of lamellipodial and filopodial protrusions containing focal adhesion kinase (FAK) which provide a substrate for other cytosolic proteins such as Src and interact with actin-associated cytoplasmic components. Recently it has been shown that the migration of vascular smooth muscle cells of arteries *in vivo* is more subtle, and is limited to elongation of tape in smooth muscle cells and an increase in cellular overlap. It is thought that cytoskeletal rearrangements in subsequent force generation play a central role in these changes. The exact cellular signalling system is still unclear. Integrin  $\alpha V\beta 3$  is necessary for the pressure-induced inward remodelling process but the rest of the biochemical sensing mechanism is still unclear. If the physiological response to a raised blood pressure in small arteries is eutrophic inward remodelling, then the integrity of the circulation appears to be preserved until this breaks down. As indicated previously, in the TGR(mREN2)27 rat there is evidence of the development of vascular wall hypertrophy in small arteries from week 6 onwards. This rat model of hypertension develops a severe form of the disorder, and indeed dams are unable to breed if they do not receive antihypertensive medication. Therefore, against this background it would appear that the breakdown of autoregulation (at the myogenic tone) is associated with the vascular wall developing a growth response (hypertrophy) in an attempt to offset the increased wall stress. Recent work on the small blood vessels of patients with type 2 (maturity onset) diabetes mellitus has demonstrated that there is vascular wall

hypertrophy. These patients were selected as already having evidence of downstream target-organ damage because they demonstrated microproteinuria and their myogenic tone was disordered (34). In other words, the onset of hypertrophy is a consequence of disruption of normal myogenic tone and the delivery of blood at a higher perfusion pressure causing cellular damage. In the kidney, this would inevitably lead to a loss of filtration capability and protein leak. In terms of cardiovascular risk, recent data from Italy have demonstrated that there is an increased risk of development of cardiovascular events in patients whose small arteries demonstrate hypertrophy rather than eutrophic inward remodelling (35). *In vitro* studies support these considerations. It has been demonstrated that the myogenic response of the middle cerebral artery from pre-stroke spontaneously hypertensive stroke-prone rat (SHRSP) are impaired compared with the spontaneously hypertensive rat (SHR) (36). This observation would explain the deranged cerebral autoregulation that has been observed in the SHRSP before stroke occurs. Also, this is associated with a redistribution of collagen throughout the blood vessel wall. Other studies have demonstrated that the myogenic component of renal autoregulation is impaired in the fawn-hooded rat (FHR) (the tubuloglomerular feedback component of renin autoregulation is unchanged) compared with controls, thereby causing glomerular hypertension and hyperfiltration, which explains why the kidneys are susceptible to the deleterious effects of moderate hypertension (37). Furthermore, the Brown Norway rat is normotensive but has a greater than normal life expectancy. However, when hypertension is induced, these animals have a high incidence of cerebral haemorrhage and mortality compared with the Long-Evans rat (38). Also, the Brown Norway rat is very sensitive to hypertension-induced renal injury, and recently the myogenic component of renal autoregulation has been found to be abnormal in normotensive Brown Norway rats (39). *In vitro* studies have demonstrated that the myogenic properties of middle cerebral arteries from the Brown Norway rat are impaired compared with the Long Evans, which would explain the susceptibility of the Brown Norway rat to hypertension-induced cerebral haemorrhage (40). Inhibition of the renin-angiotensin system markedly delays the development of cerebral haemorrhage and mortality in salt-loaded SHRSP (41). In the FHR, early angiotensin-converting enzyme (ACE) inhibition prevents renal damage, and this protection is associated with a normalisation of glomerular pressure (42). The protective effect of ACE inhibition in the kidney has been presumed to be a consequence of an inhibition of angiotensin II-induced efferent arteriolar myogenic tone. Of course, it could be argued that the effects of blood pressure lowering would be important on stroke development, and in consequence ACE inhibition is working by its antihypertensive effects. However, dexamethasone or thyroxine increased blood pressure in the SHRSP to a greater extent than salt loading but stroke does not occur (43). Also, the anti-stroke effect of captopril on salt-loaded SHRSP which occurs without an antihypertensive effect is unchanged when blood pressure is increased with dexamethasone (43). Therefore, it seems that the renin-angiotensin system inhibition improves myogenic responses, and survival in salt-loaded SHRSP is largely independent of changes in blood pressure, although this remains to be confirmed.

## SMALL ARTERY FUNCTION

There is little evidence to suggest that hypertension is associated with abnormalities of contractile function. Both *in vitro* and *in vivo* studies have suggested that contraction is normal, although there is controversy about whether the structural alterations in the vascular wall lead to exaggerated constriction and vascular amplification. This has been the subject of intense debate over a number of years, although some work in intact animals seems to suggest that vascular amplification seen in isolated vascular beds is not something observed when the whole of the circulation is integrated and examined. Again, it is controversial as to whether vascular relaxation is abnormal in hypertension. The problem with interpreting studies which have been published is that many other risk factors are often abnormal and accompany hypertension. For example, there is often associated dyslipidaemia, and there is clear evidence that oxidised LDL can reduce the bioavailability of NO. As a result of this there is evidence of abnormal endothelium-dependent dilator function which has been reported in patients with high blood pressure and dyslipidaemia, patients with dyslipidaemia and coronary artery disease, or the subcutaneous vasculature of patients with hypercholesterolaemia (44). In addition, endothelial function is recognised to decline as individuals age and therefore it is obviously complex to dissect out whether endothelial function is abnormal as a result of hypertension *per se* or as a result of other demographic abnormalities and the cohorts being examined. The overall impression that one is left with is that it is the level of oxidized LDL that is important in the bloodstream of individuals with hypertension and that blood pressure *per se* is not responsible for endothelial dysfunction. With regard to improvement in endothelial function, the use of statins has been demonstrated to restore endothelial integrity to near-normal as soon as the cholesterol levels are improved (44). There is also evidence that the use of ACE inhibitors or angiotensin receptor blockers can also ameliorate abnormal endothelial function. This is because hypercholesterolaemia is associated with an increased expression of a type 1 angiotensin receptor (AT1) and that the binding of angiotensin II to the AT1 receptor is associated with an increase in oxidative stress and a reduced bioavailability of NO. Animal experiments have demonstrated that the use of angiotensin receptor blockers independent of their antihypertensive effect can be associated with an improvement in endothelial function and a reduction in plaque load throughout the vasculature. This has also been demonstrated in a nonhuman primate. Of course, longitudinal experiments in man are awaited but it is clear that endothelial function can be improved with the use of angiotensin receptor antagonists and ACE inhibitors, and recent studies have demonstrated in humans that the combination of an angiotensin receptor blocker and a statin is extremely powerful for improving endothelial function.

## PERIVASCULAR ADIPOSE TISSUE

Perivascular adipose tissue may be the link between obesity and hypertension. Although fat cells or adipocytes are ubiquitously found throughout the body and often regarded as energy stores, there is evidence emerging that

fat cells are engine rooms producing a large number of metabolically active substances with both endocrine and paracrine actions. Surrounding almost every blood vessel in the human body are white adipocytes which are collectively termed perivascular adipose tissue (PVAT). It is now recognised that PVAT not only provides mechanical support for any blood vessel it invests but also secretes vasoactive and metabolically essential cytokines known as adipokines, which have the propensity to regulate vascular function. The emergence of obesity as a major challenge to our healthcare systems has contributed to the growing interest in adipocyte dysfunction with a view to discovering new pharmacotherapeutic agents to help rescue compromised PVAT function. PVAT function has been investigated in dog, pig and rat models as well as some *ex vivo*, *in vitro* studies of human blood vessels. There are a variety of different functional and structural properties of PVAT which seem to vary between species and anatomical site. A number of investigations have reported that healthy human PVAT can exert a local anticontractile or vasorelaxant effect on adjacent blood vessels, and careful pharmacological assessment has suggested that the primary adipokine responsible is adiponectin, although some workers have provided evidence for angiotensin 1–7 and hydrogen sulphide as also potentially playing a role. The exact mechanisms at work still require some clarification. Our most recent data would indicate that pivotal to the activity of adiponectin is the large calcium-sensitive potassium (BKCa) channel, which if absent leads to a loss of normal PVAT relaxing function. Elegant microelectrode studies of de-endothelialised rat mesenteric vessels have demonstrated that in constricted arteries, the hyperpolarisation to exogenous adiponectin is inhibited by selective blockade of BKCa. Also, there is evidence that stimulation of the  $\beta_3$  adrenoreceptor releases a factor which indirectly activates myocyte BKCa channels. This has been shown to be partly simulated by release of adiponectin from adipocytes after sympathetic nerve stimulation of  $\beta_3$  receptors on adipocytes (45). The pivotal role of Protein Kinase G in adiponectin release has also provided further clues to decipher the mechanism of action of the vasorelaxant factors released from PVAT (46,47). In obesity there is clear evidence for inflammation, increased oxidative stress and loss of normal PVAT anticontractile activity. Central again to this appears to be the activation of the macrophage, and models where there is a deficiency of this particular cell do not lose PVAT anticontractile function (48); furthermore, eosinophils have also been implicated in this regard (49). Sustained weight loss in obese animals leads to improvement in the PVAT vasorelaxant function, with attendant reductions in inflammatory markers (50). Weight-reducing surgery is associated with a restoration of normal anticontractile function despite patients remaining morbidly obese (51), and there is clear evidence from several laboratories that the loss of anticontractile activity can be rescued using either inhibitors of the renin–angiotensin system or antagonists of the angiotensin II receptor as well as aldosterone blockers. A direct link between PVAT function and blood pressure is difficult to establish; however, we have reported such a correlation in an animal model of obesity where weight gain was shown to correlate with damage to PVAT vasorelaxant function and an increase in blood pressure (52). The future holds enormous excitement and promise: there is the possibility of the prevention of diabetes as a result of introducing agonists

that can preserve PVAT activity, adiponectin analogues or drugs that can prevent the loss of PVAT anticontractile function as a result of improving the inflamed adipocyte environment (53,54).

## REFERENCES

- Khavandi K, Greenstein AS, Sonoyama K et al. Myogenic tone and small artery remodelling: Insight into diabetic nephropathy. *Nephrol Dial Transplant* 2009 Feb; 24(2): 361–369.
- Chang JB (ed.). *Textbook of Angiology*. Springer, New York; 2000.
- Beverly J, Hunt LP, Schachter M, Halliday A (eds). *An Introduction to Vascular Biology*. 2nd ed. Cambridge University Press, Cambridge; 2002.
- Nelson MT, Patlak JB, Worley JF, Standen NB. Calcium channels, potassium channels, and voltage dependence of arterial smooth muscle tone. *Am J Physiol* 1990 Jul; 259(1 Pt 1): C3–18.
- Busse R, Edwards G, Feletou M, Fleming I, Vanhoutte PM, Weston AH. EDHF: Bringing the concepts together. *Trends Pharmacol Sci* 2002 Aug; 23(8): 374–380.
- Rang HP, Dale MM, Ritter JM. *Pharmacology*. 4th ed. Churchill Livingstone, Edinburgh; 1999.
- Feletou M, Vanhoutte PM. EDHF: An update. *Clin Sci (Lond)* 2009 Aug; 117(4): 139–155.
- Bellien J, Thuillez C, Joannides R. Contribution of endothelium-derived hyperpolarizing factors to the regulation of vascular tone in humans. *Fundam Clin Pharmacol* 2008 Aug; 22(4): 363–377.
- Furchgott RF. Role of endothelium in responses of vascular smooth muscle. *Circ Res* 1983 Nov; 53(5): 557–573.
- Furchgott RF, Cherry PD, Zawadzki JV, Jothianandan D. Endothelial cells as mediators of vasodilation of arteries. *J Cardiovasc Pharmacol* 1984; 6(Suppl 2): S336–S343.
- Sumpio BE, Riley JT, Dardik A. Cells in focus: Endothelial cell. *Int J Biochem Cell Biol* 2002 Dec; 34(12): 1508–1512.
- Vallance P. Endothelial regulation of vascular tone. *Postgrad Med J* 1992 Sep; 68(803): 697–701.
- Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. *Proc Natl Acad Sci U S A* 1987 Dec; 84(24): 9265–9269.
- Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* 1987 Jun 11–17; 327(6122): 524–526.
- Moncada S, Vane JR. Pharmacology and endogenous roles of prostaglandin endoperoxides, thromboxane A<sub>2</sub>, and prostacyclin. *Pharmacol Rev* 1978 Sep; 30(3): 293–331.
- Widimsky J, Fejfarova MH, Fejfar Z. Changes of cardiac output in hypertensive disease. *Cardiologia* 1957; 31(5): 381–389.
- Julius SPJ. Autonomic nervous and behavioural factors in hypertension. In: Laragh JHBB (ed). *Hypertension: Pathophysiology Diagnosis and Management*. Raven Press, New York; 1990: 2083–2090.
- Lund-Johansen P. Twenty-year follow-up of hemodynamics in essential hypertension during rest and exercise. *Hypertension* 1991 Nov; 18(5 Suppl): III54–III61.
- Julius S, Pascual AV, Sannerstedt R, Mitchell C. Relationship between cardiac output and peripheral resistance in borderline hypertension. *Circulation* 1971 Mar; 43(3): 382–390.
- Esler M, Julius S, Zweifler A et al. Mild high-renin essential hypertension. Neurogenic human hypertension? *N Engl J Med* 1977 Feb 24; 296(8): 405–411.
- Esler M, Jennings G, Korner P et al. Assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. *Hypertension* 1988 Jan; 11(1): 3–20.
- Bright R. Tabular view of the morbid appearances in 100 cases connected with albuminous urine with observations. *Guy's Hospital Reports* 1836; 1: 380–400.
- Heagerty AM, Aalkjaer C, Bund SJ et al. Small artery structure in hypertension. Dual processes of remodeling and growth. *Hypertension* 1993 Apr; 21(4): 391–397.
- Korsgaard N, Aalkjaer C, Heagerty AM et al. Histology of subcutaneous small arteries from patients with essential hypertension. *Hypertension* 1993 Oct; 22(4): 523–526.
- Rizzoni D, Porteri E, Boari GE et al. Prognostic significance of small-artery structure in hypertension. *Circulation* 2003 Nov 4; 108(18): 2230–2235.
- Aalkjaer C, Heagerty AM, Bailey I et al. Studies of isolated resistance vessels from offspring of essential hypertensive patients. *Hypertension* 1987 Jun; 9(6 Pt 2): III155–8.
- Bund SJ, West KP, Heagerty AM. Effects of protection from pressure on resistance artery morphology and reactivity in spontaneously hypertensive and Wistar-Kyoto rats. *Circ Res* 1991 May; 68(5): 1230–1240.
- Zacchigna L, Vecchione C, Notte A et al. Emilin1 links TGF-beta maturation to blood pressure homeostasis. *Cell* 2006 Mar 10; 124(5): 929–942.
- Izzard AS, Heagerty AM, Leenen FH. The amplifier hypothesis: Permission to dissent? *J Hypertens* 1999 Dec; 17(12 Pt 1): 1667–1669.
- Izzard AS, Bund SJ, Heagerty AM. Increased wall-lumen ratio of mesenteric vessels from the spontaneously hypertensive rat is not associated with increased contractility under isobaric conditions. *Hypertension* 1996 Oct; 28(4): 604–608.
- Leenen FH, Yuan B, Tsoporis J, Lee RM. Arterial hypertrophy and pressor responsiveness during development of hypertension in spontaneously hypertensive rats. *J Hypertens* 1994 Jan; 12(1): 23–32.
- Heerkens EH, Shaw L, Ryding A et al. alphaV integrins are necessary for eutrophic inward remodeling of small arteries in hypertension. *Hypertension* 2006 Feb; 47(2): 281–287.
- Martinez-Lemus LA, Crow T, Davis MJ, Meininger GA. alphaV-beta3- and alpha5beta1-integrin blockade inhibits myogenic constriction of skeletal muscle resistance arterioles. *Am J Physiol Heart Circ Physiol* 2005 Jul; 289(1): H322–H329.
- Schofield I, Malik R, Izzard A et al. Vascular structural and functional changes in type 2 diabetes mellitus: Evidence for the roles of abnormal myogenic responsiveness and dyslipidemia. *Circulation* 2002 Dec 10; 106(24): 3037–3043.
- Izzard AS, Rizzoni D, Agabiti-Rosei E, Heagerty AM. Small artery structure and hypertension: Adaptive changes and target organ damage. *J Hypertens* 2005 Feb; 23(2): 247–250.
- Izzard AS, Horton S, Heerkens EH et al. Middle cerebral artery structure and distensibility during developing and established phases of hypertension in the spontaneously hypertensive rat. *J Hypertens* 2006 May; 24(5): 875–880.
- van Dokkum RP, Sun CW, Provoost AP et al. Altered renal hemodynamics and impaired myogenic responses in the fawn-hooded rat. *Am J Physiol* 1999 Mar; 276(3 Pt 2): R855–R863.
- Capdeville M, Coutard M, Osborne-Pellegrin MJ. Spontaneous rupture of the internal elastic lamina in the rat: The manifestation of a genetically determined factor which may be linked to vascular fragility. *Blood Vessels* 1989; 26(4): 197–212.
- Wang X, Ajikobi DO, Salevsky FC, Cupples WA. Impaired myogenic autoregulation in kidneys of Brown Norway rats. *Am J Physiol Renal Physiol* 2000 Jun; 278(6): F962–F969.
- Delaney PJ, Burnham MP, Heagerty AM, Izzard AS. Impaired myogenic properties of cerebral arteries from the Brown Norway rat. *J Hypertens* 2012 May; 30(5): 926–931.
- Wang H, Smeda JS, Lee RM. Prevention of stroke and preservation of the functions of cerebral arteries by treatment with perindopril in stroke-prone spontaneously hypertensive rats. *Can J Physiol Pharmacol* 1998 Jan; 76(1): 26–34.
- Versept GH, Provoost AP, Braam BB et al. Angiotensin-converting enzyme inhibition in the prevention and treatment of chronic renal damage in the hypertensive fawn-hooded rat. *J Am Soc Nephrol* 1997 Feb; 8(2): 249–259.
- Nagaoka A, Shino A, Iwatsuka H. Accelerating effects of dexamethasone and thyroxine on hypertension without accompanying stroke in stroke-prone spontaneously hypertensive rats. *Life Sci* 1979 Jan 1; 24(1): 71–77.
- Goode GK, Heagerty AM. In vitro responses of human peripheral small arteries in hypercholesterolemia and effects of therapy. *Circulation* 1995 Jun 15; 91(12): 2898–2903.
- Saxton SN, Ryding KE, Aldous RG et al. Role of sympathetic nerves and adipocyte catecholamine uptake in the vasorelaxant function of perivascular adipose tissue. *Arterioscler Thromb Vasc Biol* 2018 Apr; 38(4): 880–891.
- Withers SB, Simpson L, Fattah S et al. cGMP-dependent protein kinase (PKG) mediates the anticontractile capacity of perivascular adipose tissue. *Cardiovasc Res* 2013 Jan 1; 101(1): 130–137.
- Withers SB, Bussey CE, Saxton SN et al. Mechanisms of adiponectin-associated perivascular function in vascular disease. *Arterioscler Thromb Vasc Biol* 2014 Aug; 34(8): 1637–1642.
- Withers SB, Agabiti-Rosei C, Livingstone DM et al. Macrophage activation is responsible for loss of anticontractile function in inflamed perivascular fat. *Arterioscler Thromb Vasc Biol* 2011 Apr; 31(4): 903–913.

49. Withers SB, Forman R, Meza-Perez S et al. Eosinophils are key regulators of perivascular adipose tissue and vascular functionality. *Sci Rep* 2017 Mar 17; 7: 44571.
50. Bussey CE, Withers SB, Aldous RG et al. Obesity-related perivascular adipose tissue damage is reversed by sustained weight loss in the rat. *Arterioscler Thromb Vasc Biol* 2016 Jul; 36(7): 1377–1385.
51. Aghamohammadzadeh R, Greenstein AS, Yadav R et al. Effects of bariatric surgery on human small artery function: Evidence for reduction in perivascular adipocyte inflammation, and the restoration of normal anticontractile activity despite persistent obesity. *J Am Coll Cardiol* 2013 Jul 9; 62(2): 128–135.
52. Aghamohammadzadeh R, Unwin RD, Greenstein AS, Heagerty AM. Effects of obesity on perivascular adipose tissue vasorelaxant function: Nitric oxide, inflammation and elevated systemic blood pressure. *J Vasc Res* 2015; 52(5): 299–305.
53. Aghamohammadzadeh R, Withers S, Lynch F et al. Perivascular adipose tissue from human systemic and coronary vessels: The emergence of a new pharmacotherapeutic target. *Br J Pharmacol* Feb; 165(3): 670–682.
54. Aghamohammadzadeh R, Heagerty AM. Obesity-related hypertension: Epidemiology, pathophysiology, treatments, and the contribution of perivascular adipose tissue. *Ann Med* 2012 Jun; 44(Suppl 1): S74–S84.



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## INTRODUCTION

Cardiovascular diseases (CVD), including coronary artery disease and stroke, collectively remain the leading cause of death in the world, with heart disease and stroke representing the leading two killers (1). Although the clinical manifestations of CVD appear from middle age, over the last 40 years it has become clear that the initiation and progression of disease depends on profound dynamic changes in vascular biology that begin many years before and are influenced by exposure to risk factors, including hypertension, obesity, dyslipidemia and smoking as well as by the presence of specific diseases, such as diabetes mellitus.

The endothelium consists of a cellular monolayer that covers the inner surface of all vessels in the cardiovascular system, and because of its position, it is optimally placed to act as a signal transducer of the injurious activity of cardiovascular risk factors on the vascular wall. Initially considered a simple tapestry localised between the bloodstream and the vascular wall, it is now clear that it has key functions in regulating vascular homeostasis through the production of a wide range of factors that regulate vascular tone, cellular adhesion, thromboresistance, smooth muscle cell proliferation and vessel wall inflammation. As such, it represents the largest autocrine-paracrine organ in humans (2).

In a quiescent state, the endothelium exerts several anti-atherosclerotic functions, ensuring a constant vasodilatory tone, protecting from activation of the coagulation system, contrasting migration of inflammatory cells from the bloodstream to the intima and suppressing proliferation of smooth muscle cells (2). While a variety of molecules are involved in regulating these functions, the most important is nitric oxide (NO). The historical demonstration by Furchgott and Zawadzki that removal of the endothelium abrogates the *in vitro* vasodilator effect of acetylcholine (3) led to the identification 30 years ago of NO as a major endogenous local regulator of vascular tone (4–7). This gas is generated from L-arginine by the action of endothelial NO synthase (eNOS) in the presence

of cofactors such as tetrahydrobiopterin (8). Shear stress, namely tangential cyclic stress generated on vascular walls by blood flow, is a key activator of eNOS in normal physiology (9), making possible a continuous adaptation of the peripheral organ perfusion to changes in cardiac output. In addition to mechanical stimuli, the eNOS may be activated by signalling molecules such as bradykinin, adenosine, vascular endothelial growth factor (in response to hypoxia) and serotonin (released during platelet aggregation) (10). Other endothelium-derived relaxing factors include prostacyclin and the production of various endothelium-derived hyperpolarising factors (EDHFs), representing a compensatory vasodilating pathway acting in those clinical conditions characterised by a reduced NO availability (11,12).

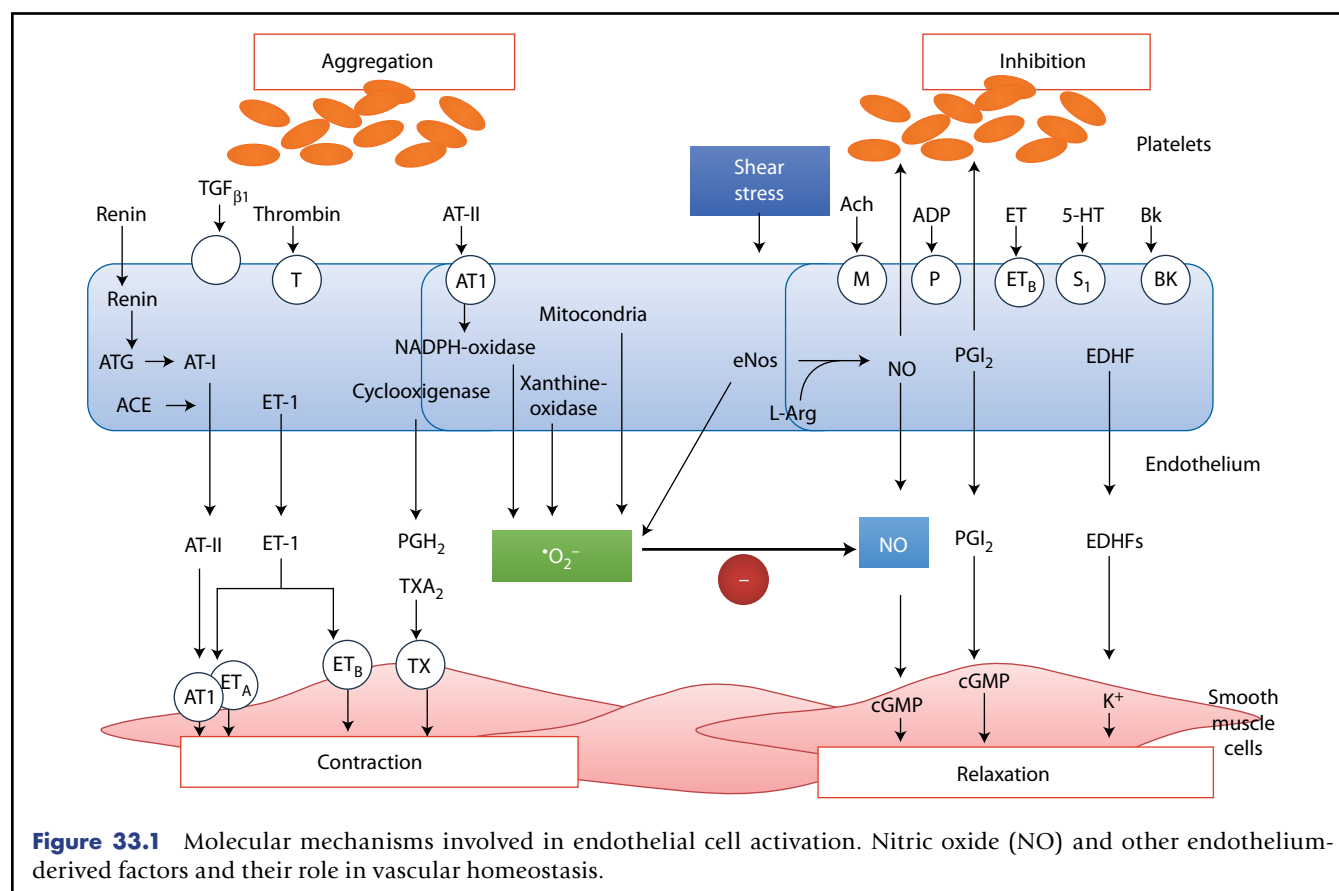
## ENDOTHELIAL ACTIVATION, DAMAGE AND REPAIR

### MECHANISMS OF DAMAGE

When exposed to cardiovascular risk factors or mechanical injuries, the endothelium undergoes activation, resulting in several changes of its internal biological machinery. This state, which represents the earliest manifestation of an altered vascular biology due to cardiovascular risk factor exposure, is known as endothelial dysfunction and is characterised by a reduced NO availability in the vascular wall (13). Endothelial dysfunction was first described in human hypertension in the forearm vasculature in 1990 (14). Impaired vasodilation has been since documented in type 1 and type 2 diabetes, hypercholesterolaemia, smoking, obesity, physiological ageing and several diseases, including coronary artery disease, congestive heart failure, chronic renal failure, rheumatic and other chronic inflammatory diseases (e.g. periodontitis) (13,15).

The reduced availability of NO observed in most of these conditions was thought to depend upon a switch in signalling from a NO-mediated silencing of cellular processes toward activation by redox signalling (Figure 33.1). Reactive oxygen species (ROS), mainly superoxide anions, are unstable molecules that can rapidly bind NO to form the highly reactive intermediate peroxynitrite (ONOO<sup>-</sup>). Thus, endothelial dysfunction is characterised by an increased consumption of NO and formation of nitroso-compounds (16). This has multiple negative effects: reducing NO availability, having direct vasoconstrictor and cytotoxic effects and impairing the activity of the eNOS (16). Various enzymatic and non-enzymatic sources of ROS have been described to be activated in dysfunctional endothelial cells, smooth muscle cells and inflammatory cells within the arterial wall of patients exposed to cardiovascular risk factors, including nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, cyclooxygenase, xanthine oxidase and the same eNOS (17) (Figure 33.1). The latter can contribute to ROS generation when uncoupled, producing either anion superoxide when there is a deficiency of its key cofactor tetrahydrobiopterin, or hydrogen peroxide when its substrate L-arginine is deficient (18). Mitochondria ROS (mtROS) has been identified as a major contributor to cellular ROS during endothelial cell activation. mtROS is generated at Complex I and Complex III in the mitochondrial electron transport chain (19) and, while historically considered a toxic by-product of mitochondrial metabolism, recent evidence suggests that it can act as a signalling molecule, directly contributing to proinflammatory

cytokine production (20). The contribution of mtROS to the global levels of ROS within endothelial cells might be particularly important in some conditions, including obesity and diabetes mellitus as well as in physiological ageing. In obesity and diabetes mellitus, an altered balance between nutrient availability and demand for ATP in favour of the former might cause a decrease in the rate of electron flow that prolongs the lifespan of reactive intermediates at Complexes I and III, ultimately producing a higher amount of superoxide anion (19,21). In ageing, instead, several pieces of evidence suggest that the mitophagy, the mechanism used by cells to eliminate damaged and dysfunctional mitochondria, is defective, leading to accumulation of dysfunctional mitochondria that produce a larger amount of mtROS during their physiological activity (22). Recent evidence seems to confirm the key role of mtROS in mediating endothelial cell dysfunction by reduction of NO availability. In diabetic patients, circulating leukocytes and arterioles isolated from subcutaneous fat display higher mitochondrial ROS production and membrane hyperpolarisation (23,24). Furthermore, impaired endothelium-dependent vasodilation in freshly isolated arterioles from patients with diabetes is reversed by mild membrane depolarisation or mitochondria-targeted antioxidants (23). Vascular dysfunction with age is a consequence of excessive superoxide-related oxidative stress, much of which is of mitochondrial origin (25). Preclinical findings show that oral supplementation of MitoQ (a potent mitochondrial targeted antioxidant) restores age-related decrease of endothelial-dependent vasodilation in old mice (25),



and similar results have been reported in skeletal muscle feed arteries biopsied from older adult humans (26). Collectively, this evidence suggests that mtROS might represent an important therapeutic target to prevent or reduce endothelial cell damage related to exposure to some cardiovascular risk factors.

In the attempt to compensate for NO deficiency, endothelium-dependent vasodilation is partially maintained by the production of endothelium-derived vasodilators other than NO, such as prostanoids and other endothelium-derived hyperpolarising factors (27). Endothelin-1 (ET-1), by contrast, is a potent vasoconstrictor and mitogenic peptide produced by endothelial cells, the expression of which is normally upregulated in conditions of endothelial dysfunction. In essential hypertension, for example, it is possible to observe a relative increase of ET-1 vasoconstrictor tone compared to the vasodilatory effects of NO (28) (Figure 33.1).

Activated endothelial cells increase their expression of selectins, VCAM-1, and intercellular adhesion molecule-1 (ICAM-1) (29,30). These molecules promote the adherence and migration of monocytes from the bloodstream to the subendothelial space, representing early events in the formation of the atherosclerotic lesions (31) (Figure 33.2).

With prolonged or repeated exposure to cardiovascular risk factors, the chronic activation of endothelial cells and the switch to a pro-oxidant phenotype of the intracellular machinery may exhaust the capacity of cellular enzymatic and nonenzymatic antioxidants, inducing further progression of the endothelial damage. In these conditions, the excess of ROS compared to the reduced antioxidant capacity can promote the interaction of ROS with all major intracellular macromolecules (lipids, proteins and nucleic acids), favouring the loss of cellular integrity and early cellular ageing. The increased formation of peroxynitrite ( $\text{ONOO}^-$ ) (Figure 33.2), resulting from the

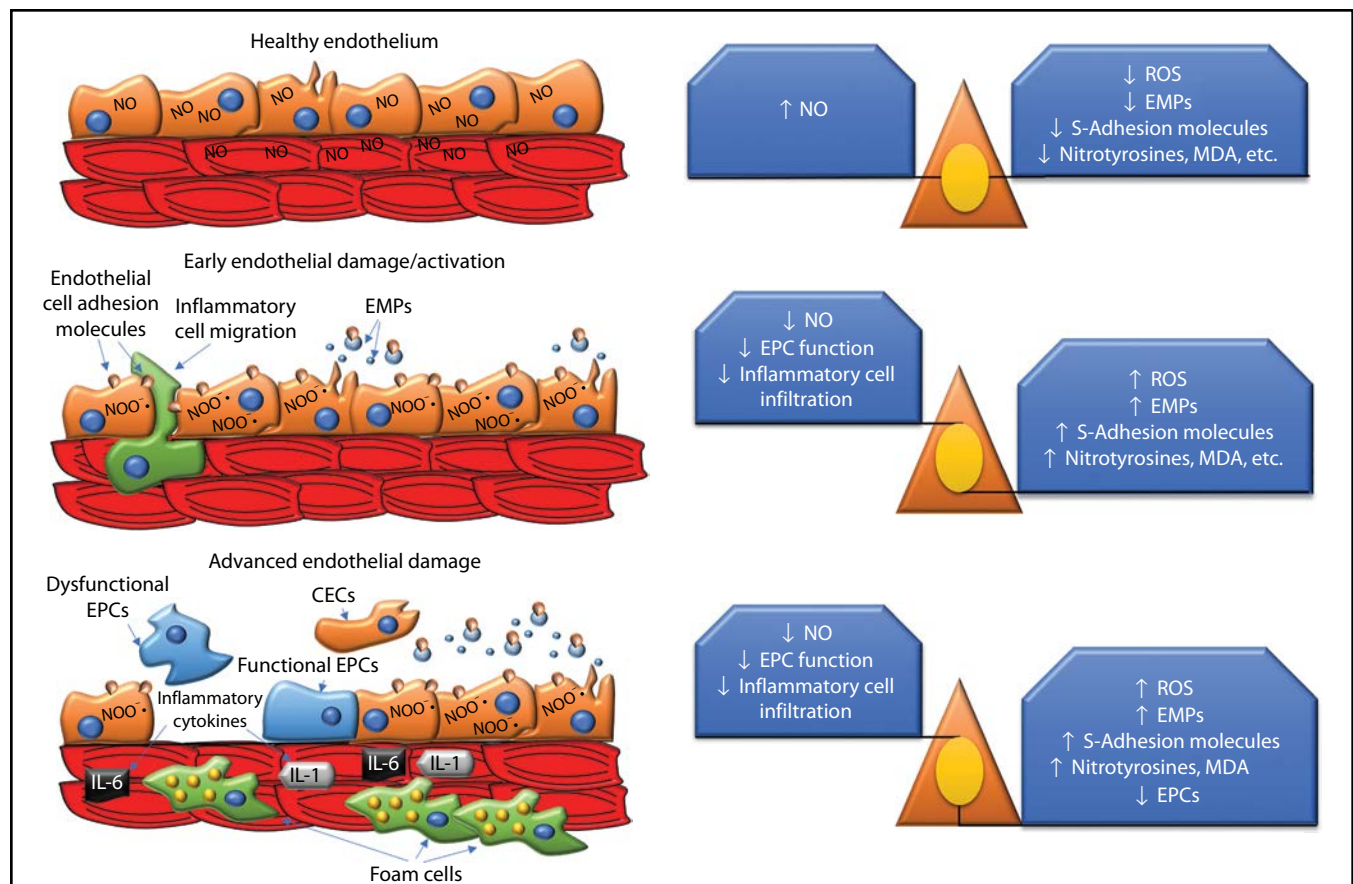


**Figure 33.2** Progression of endothelial damage. In normal vascular physiology, nitric oxide (NO) plays a key role in maintaining the vascular wall in a quiescent state by inhibition of inflammation, cellular proliferation and thrombosis. Exposure to cardiovascular risk factors switches the signal toward a pro-oxidant/-inflammatory state. Endothelial cells adopt an activated phenotype, characterised by reduced NO availability, increased production of nitroperoxides ( $\text{NOO}^\bullet$ ) and expression of cellular adhesion molecules. These events promote migration of inflammatory cells in the subendothelial space and lead to initial endothelial cell damage, with release of endothelial microparticles (EMPs). In cases of prolonged and/or repeated exposure to cardiovascular risk factors, endothelial cell damage progress leads to endothelial cell senescence. Damaged endothelial cells detach from the vascular wall (circulating endothelial cells [CECs]) and are only partially replaced by endothelial progenitor cells (EPCs) due to their dysfunctional/aged phenotype. This promotes accumulation of further inflammatory cells in the subendothelial space that, following accumulation of lipids, sustains the local inflammatory process by producing proinflammatory cytokines. This sequence of events ultimately leads to plaque formation.

interaction between ROS and NO, leads to nitrosylation of cellular proteins, forming nitrotyrosine. This is used as a robust marker of cellular oxidative stress (32–34), and its concentration is increased after exposure of endothelial cells to several activating stimuli (including TNF- $\alpha$  (35), oxidized LDL (35), hypoxia (36) and altered shear stress (37)) as well as with ageing in animal models (38–40) and in arterial endothelial cells of humans (41). In addition to the nitration of tyrosine, which is irreversible, aged arteries also exhibit markers of lipid peroxidation such as 4-hydroxynonenal (4-HNE) or malondialdehyde (MDA) and/or another reversible regulatory oxidative stress marker, glutathionylation, at cysteine residues (42–45). The ROS-mediated damage to major intracellular components alters several cellular functions, ultimately resulting in endothelial cell senescence or apoptosis and detachment of endothelial cells from the vascular wall.

Circulating markers of this endothelial damage include endothelial microparticles (EMPs), and whole endothelial cells (46,47) (Figure 33.2). Microparticles (MPs) are cell membrane-shedded submicron fragments ranging from 0.1–1.0  $\mu\text{m}$  containing information such as mRNA, microRNAs (miRNAs), receptor, and specific proteins of the parent cell. MPs are expressed by cells during cellular stress and activation (48). Like other microparticles, endothelial microparticles (EMPs) are anucleated vesicles formed following cytoskeletal and membrane reorganisation, released in response to cell activation, injury, angiogenesis/neovascularisation and/or apoptosis (49). Ischaemia (50), TNF- $\alpha$  (51), other inflammatory cytokines (52), reactive oxygen species (52), plasminogen activator inhibitor (53), thrombin (54), camptothecin (55), C-reactive protein (56) and uremic toxins (57) can induce in vitro EMP generation. Conversely, endogenous NO dampens the release of EMPs produced after stimulation with C-reactive protein (56). Previous studies found elevated EMPs in several disease conditions, including pre-eclampsia (58,59), severe hypertension (60), acute coronary syndromes (61) and stroke (62). In patients with documented endothelial dysfunction, levels of circulating EMP are inversely correlated with the amplitude of flow-mediated dilatation, independently of age and blood pressure values (63–66). This evidence suggests EMPs represent a reliable marker of pathological processes involving the endothelium. Initially, EMPs were simply considered markers of endothelial cell activation and damage. More recently, it became clear that EMPs can play a major role in inflammation, thrombosis and angiogenesis (67). These functions are mediated by the array of diverse molecules on their surface (with functions encompassing coagulation, cell survival, inflammation, enhanced oxidative stress, adhesion, proteolysis, remodelling, angiogenesis and tumour growth), as well as by their intracellular proteins, nucleic acids and organelles. Once released into circulation, EMPs can thus exert functional effects on cellular targets through surface membrane interactions and/or fusion and delivery of its intravesicular cargo (68).

Circulating endothelial cells (CECs) are another marker which has been used to quantify endothelial damage, considering their number directly relates to the amount of apoptotic endothelial cells in the vascular wall (69) (Figure 33.2). They were first detected in the 1970s in smears of peripheral blood on the basis of their presumed morphology (70). The mechanism of circulating endothelial cell detachment is only partially understood and is complex, involving many factors, such as mechanical injury, the

classic risk factors for atherosclerosis, alteration of endothelial/subendothelium cellular adhesion molecules, defective binding to anchoring matrix proteins, and cellular apoptosis with decreased survival of cytoskeletal proteins (69,71,72). In normal steady-state conditions, the number of CECs in the bloodstream is very low, as endothelial turnover is a very slow process in the absence of pathological stimuli, and nonviable CECs are rapidly cleared by the reticuloendothelial system. The level of CECs is expected to increase as a consequence of any type of damage to the vessel wall (73). Indeed, several studies have demonstrated an increased number of CECs in patients with numerous clinical conditions characterised by vascular involvement, ranging from cardiovascular risk factors (e.g. diabetes mellitus) (74), immune-mediated vasculitides (75) and sickle cell disease crisis (76) to systemic infections (77). Based on this background, the level of CECs can be taken to represent an indicator of the ongoing systemic endothelial damage. While the number of CECs was considered a promising marker to characterise endothelial damage and the risk of cardiovascular disease until a few years ago, several drawbacks have limited its development in clinical practice. Firstly, their very low numbers and complex phenotype make their detection extremely difficult in peripheral blood, and several published techniques have shown different degrees of variability, reporting a wide range of CEC values (0–7900 CEC/mL) in healthy subjects (78–82). Secondly, CECs may also derive from sites of incompetent angiogenesis, where tissue endothelial cells proliferate and organise into immature leaky tubular structures that come into contact with the bloodstream (83). In these cases, CECs might represent a marker of endothelial cell proliferation rather than damage. Moreover, enhanced release of CECs might also take place during normal body growth or at sites of tissue regeneration, either physiological (e.g. after menstruation) or pathological (e.g. wound healing). Because of these limitations, the importance of CEC as markers of endothelial damage has been reconsidered, and not many studies have been published exploring their capacity to predict evolution or reflect the severity of cardiovascular disease or endothelial dysfunction.

## MECHANISMS INVOLVED IN ENDOTHELIAL REPAIR

The severity of endothelial damage depends not only on the extent of the injury, but also on the endogenous capacity for repair. While endothelial cells can replicate locally and replace those lost or damaged after endothelial injury, it has been suggested that this mechanism of repair is not efficient enough to ensure endothelial integrity, particularly when the endothelium is chronically exposed to the injurious action of cardiovascular risk factors (84). Over the last 20 years, circulating endothelial progenitor cells (EPCs) have been identified as an effective and alternative mechanism for maintenance and repair of the damaged endothelium (85) (Figure 33.2). Endothelial progenitor cells originating from either bone marrow or other tissues (e.g. spleen, vessel wall, adipose tissue, placenta, etc.), have been classified into hematopoietic and nonhematopoietic progenitor cells (86). Several different phenotypes of EPCs have been identified based on the expression of different surface antigens. Importantly, EPCs with different surface phenotypes have shown the capacity to influence multiple



aspects of the vascular biology, suggesting that these cells might have pluripotent functions and that their functional destiny is defined by the biological niche where they are called to operate. Irrespective of their origins and multiple influences on the vascular biology, the most important characteristic of these cells is that they are capable of differentiating into endothelial cells under specific conditions (85,87,88) and can contribute to the formation of capillary-like networks (89). Multiple factors (cytokines released by target tissue, growth factors, sex hormones, etc.) mobilise EPCs to migrate from the bone marrow stroma into the blood circulation. As one of the most important factors regulating EPC mobilisation is NO and the activity of eNOS (90), the number of recruited EPCs can be impaired in patients with cardiovascular risk factors, thus contributing to the endothelial damage by reducing the repair capacity of the endothelial monolayer. Indeed, the number of circulating EPCs is negatively associated with the Framingham risk score (91) and positively related to endothelial function assessed at the level of both brachial (91) and coronary arteries (92) in healthy subjects (91) as well as in patients with coronary artery disease (93). The capacity of EPC to reflect endothelial health and damage is also confirmed by the evidence that many drugs used in cardiovascular prevention and able to improve endothelial function also show positive effects on the circulating number of EPCs (94). Thus, current evidence supports the hypothesis that a reduced number of EPC marks both a deficient vascular repair and a state of endothelial damage.

## METHODS FOR ASSESSING ENDOTHELIAL FUNCTION/DAMAGE

### VASCULAR REACTIVITY TESTS

Early endothelial damage expressed in altered endothelial function is usually assessed by vascular reactivity studies (95), defining the severity of the compromised response of the endothelial cells to stimulating or inhibiting substances in several vascular regions and measuring the vessel changes induced by experimental perturbation. Responses can be evaluated in the macrocirculation (brachial, radial, femoral and epicardial arteries) and microcirculation (peripheral muscle, subcutaneous or skin tissue, coronary microcirculation).

### CORONARY EPICARDIAL AND MICROVASCULAR FUNCTION

The first demonstration of endothelial dysfunction was obtained in atherosclerotic epicardial vessels by the intracoronary infusion of acetylcholine in 1986 (96). Although tests of endothelial function in the coronary arteries are highly limited by their invasive nature, they have the advantage to define the endothelial status directly in this important vascular bed.

#### EPICARDIAL ARTERIES

Quantitative angiography allows assessment endothelium-dependent response of coronary circulation at the level of pericardial vessels (usually in the left descending artery) by measuring coronary blood flow during the

intracoronary infusion of substances that can cause vasodilation through endothelial-dependent (acetylcholine) or -independent pathways (nitrates, papaverine). While in healthy subjects the intracoronary infusion of endothelial agonists produces vasodilation, a paradoxical vasoconstriction to acetylcholine of the epicardial arteries is commonly observed in the presence of endothelial dysfunction, due to the direct effect of the stimulating factor on the smooth muscle rather than the endothelial cells (96). This response was observed in essential hypertensive patients also in the absence of angiographically detectable lesions (97–99).

In healthy arteries, stimulation of endothelial  $\alpha_2$ -adrenergic receptors due to activation of the sympathetic nervous system leads to release of NO and endothelium-derived hyperpolarising factors, resulting in vasodilation. In the presence of endothelial dysfunction, by contrast, the activation of  $\alpha_1$ -adrenergic receptors on smooth muscle cells dominates the vascular response to the sympathetic stimulation. Thus a reduced vasodilation with papaverine administration (100), exercise (101) or cold pressure test (102) is observed in patients with hypertension, mirroring the responses to acetylcholine (103).

### CORONARY MICROCIRCULATION

The measurement of coronary blood flow by Doppler flow wires enables assessment of endothelial function in the coronary microcirculation by quantitative angiography during the intracoronary infusion of various endothelium-dependent (acetylcholine and substance P) or -independent (sodium nitroprusside and nitroglycerin) vasodilators (104). The concomitant intracoronary infusion of  $N^G$ -mono-methyl-L-arginine (L-NMMA, a potent inhibitor of the eNOS) also provides the opportunity to establish the proportion of the vasomotor response due to the activity of the eNOS and thus the NO availability (105). Although this test directly assesses coronary circulation, its invasive nature limits its use to patients with advanced disease and precludes repeated testing during serial follow-up. While other, noninvasive techniques are available to assess endothelial function of the coronary microvasculature (including positron emission tomography, myocardial perfusion imaging and echocardiography) (104), the radiation exposure, the reduced availability of the machines used for their assessment, the questionable reproducibility and the need for systemic administration of endothelial agonists and antagonists limit their use in clinical practice. Nevertheless, it was shown that endothelial function in coronary microcirculation has prognostic value in patients with established coronary disease (100).

### PERIPHERAL TECHNIQUES FOR ASSESSING ENDOTHELIAL FUNCTION

#### FLOW-MEDIATED DILATION OF THE BRACHIAL ARTERY

The flow-mediated dilation (FMD) of the brachial artery is currently considered the gold standard, noninvasive technique for the assessment of endothelial function in vivo. It measures the changes of the diameter of the brachial artery induced by the reactive hyperaemia which follows 5-minute forearm ischemia induced by the blood pressure cuff applied to the forearm (106) (Figure 33.3). The increased shear stress induced by the hyperaemia on the vascular wall results in a local endothelial release of





**Figure 33.3** Flow-mediated dilation. Lab setup (left) and automated edge-detection system (right). (Adapted by permission from Bruno RM, Picano E. *Endothelial Function in the Stress Echocardiography Laboratory*. Springer, Cham; 2015 (181).)

NO (107), which induces a vasodilation in a dose-dependent fashion. Endothelium-independent vasodilatory response can be tested by low-dose sublingual nitroglycerin. Because of its noninvasive nature, the presence of clear indications to standardise each acquisition and its high intra- and interobserver reproducibility, FMD has been widely used in clinical research, testing the impact of lifestyle and pharmacological interventions on endothelial function in both adults and children, particularly in the early preclinical stage of the disease when the alterations of the vascular biology are more likely to be reversible (108).

The greatest challenges of this technique include the need for highly trained operators, the recruitment of large study populations for clinical studies due to the variability and degree of response, the expense of the equipment (which not only includes the ultrasound machine but also a clamp to hold and adjust probe position, as well as a computerized system to automatically measure brachial artery diameter to minimize its variability) and the care required to minimize the effect of environmental or physiological influences (109,110). However, following standardised protocols and with appropriate training, FMD has been shown its high reproducibility also in multicentre studies (111,112).

#### TECHNIQUES USED TO ASSESS ENDOTHELIAL FUNCTION IN THE PERIPHERAL MICROCIRCULATION

While several techniques have been developed to measure microvascular endothelial function in the peripheral microcirculation, the most validated and widely used include EndoPAT, forearm plethysmography and micromyography.

##### ENDOPAT

This device has been developed to provide observer-independent measures of pulsatile arterial volume changes by plethysmography (113). Using peripheral arterial tonometry, the machine captures beat-to-beat recordings of the finger arterial pulse wave amplitude with pneumatic probes. Following the same principles as FMD, a pressure cuff is placed on one forearm and inflated to a suprasystolic pressure to produce 5 minutes of ischaemia followed by reactive hyperaemia. The pneumatic probe applied to

the fingertip of the same arm records the increase in arterial blood volume, which is reflected by an increase in pulsatile arterial column changes. To account for any systemic drift in vascular tone during the test, the central device corrects this acquisition with the recordings obtained from a pneumatic probe applied to the contralateral arm, where no stimuli are applied.

While digital vascular dysfunction is associated with traditional and metabolic cardiovascular risk factors (114), several concerns have been raised about the capacity of this index to reflect endothelial function, as augmentation of the pulse amplitude after reactive hyperaemia involves changes in flow and in digital microvessel dilatation that are only partly dependent on NO (115). Two large cross-sectional studies (114,116) showed modest associations between FMD and EndoPAT, suggesting that these two methodologies are likely measuring different aspects of vascular biology.

##### FOREARM PLETHYSMOGRAPHY

By means of a strain-gauge applied to the distal part of the forearm and a blood pressure cuff positioned in the distal part of the arm which stops the venous outflow, this technique measures the changes in the forearm blood volume induced by intra-arterial infusion of endothelial agonists performed from a small polyethylene cannula inserted in the brachial artery. As the venous outflow is occluded during each recording, any change in blood volume induced by infusion of an endothelial agonist reflects the change in peripheral vascular resistances (reduced peripheral resistances = increase in flow = increased blood volume) due to the stimulation of endothelial cell function. Based on these assumptions, endothelium-dependent vasodilation is estimated by a dose-response curve to intra-arterial infusion of endothelial agonists (i.e. acetylcholine, bradykinin, methacholine, etc.), while endothelium-independent vasodilation is obtained by a dose-response curve to intra-arterial sodium nitroprusside (117). Concomitant infusion of L-NAME or vitamin C enables assessment of the proportion of the endothelial response, which is dependent on the activity of eNOS or the local amount of oxidative stress (118).

When studies are conducted in a quiet, temperature-controlled room (22–26°C), with the subject resting in a

comfortable supine position, measurement of forearm blood flow by strain gauge plethysmography compares favourably with values obtained by other established techniques (119,120). As this approach allows infusion of drugs at systemically ineffective rates, the forearm technique provides the capacity to explore the mechanisms underlying the endothelial dysfunction related to the exposure to different cardiovascular risk factors, including hypertension (27,121,122). On the other hand, the limitation of the forearm technique is its invasiveness (limiting the number of patients enrolled and the possibility to repeat testing frequently) and that is time-consuming (due to the complexity of the experimental design in assessing dose-response curves to agonists and antagonists).

#### MICROMYOGRAPHY

Micromyography was developed by Mulvany and Halpern in the 1970s (123) and it was subsequently applied to vascular segments obtained from several animal models of hypertension, and in several vascular districts (mesenteric, cerebral, coronary, renal, femoral, etc.) (124). There are two major variants of this technique: wire micromyography and perfusion-pressure micromyography. Both techniques allow investigation of morphological and functional characteristics of isolated resistance arterioles (lumen diameter 150–300  $\mu\text{m}$ ), taken from subcutaneous tissue obtained by skin biopsies. Once cleaned of adherent connective tissue, vessels can be investigated with the wire myograph or the pressurised myograph. Briefly, the first technique implies that two wires are threaded through the vessel, while in the pressurised system the artery is slipped into two glass microcannulae and exposed to a constant pressure (124). Once mounted on the myograph, a dose-response curve to acetylcholine is generated, and the amount of vascular relaxation is quantified by a software. The perfusion-pressure micromyography allows application of different substances and transfection of small interfering RNA (siRNA) (125,126) on the mounted arteries, thus enabling exploration of their effect on the endothelial-dependent vasodilation. As such, this technique enables identification of the potential pathways involved in endothelial dysfunction in different pathological conditions.

#### CIRCULATING MARKERS

As the endothelial damage seems to be directly involved in the initiation, evolution and complications of atherosclerosis, the availability of markers easily measured in the peripheral circulation which could inform on the severity of the endothelial damage could carry several advantages and help the risk stratification of patients with hypertension. Indeed, assessment of direct products of endothelial cells that change when the endothelium is activated has been suggested to refine patient risk stratification (127). While this is a promising prospective, many of these circulating markers are currently difficult and expensive to measure. The additional challenges posed by the variability of the methods used for their assessment makes translation to the clinical practice of the research evidence accumulated thus far very difficult.

#### SOLUBLE MARKERS OF ENDOTHELIAL CELL ACTIVATION/DAMAGE

An increase in soluble markers of endothelial cell activation and injury have been identified in subjects with

different cardiovascular risk factors and various manifestations of cardiovascular disease. While endothelial leukocyte adhesion molecules, including E-selectin, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) reflect activation of the endothelium, either specifically (sE-selectin) or nonspecifically (sVCAM-1, sICAM-1) (128), thrombomodulin (a protein C cofactor with anticoagulant activity) is released from injured endothelial cells and its soluble levels have been shown to be a specific marker of endothelial cell damage (129). Soluble levels of thrombomodulin are associated with severity of coronary artery disease, stroke or peripheral occlusive arterial disease, while are not increased in healthy or asymptomatic subjects (127). von Willebrand factor (vWF) is another protein expressed by activated endothelial cells that acts as an endothelial ligand for platelet glycoproteins. vWF plays a vital role in mediating platelet adhesion to damaged arterial walls (130). Injured endothelial cells release vWF from endothelial Weibel – Palade bodies; thus vWF is considered a marker of endothelial damage, which is increased in cardiovascular diseases and predicts risk for ischaemic heart disease or stroke (131). All these proteins can be easily measured in the peripheral blood using ELISA kits, and their assessment requires minimal amounts of blood.

#### CECs, EMPs AND EPCs

Flowcytometry and immunobeads assays are the two techniques used to assess the number of CECs. In the flowcytometry assay, the whole blood or peripheral blood mononuclear cells are stained using monoclonal antibodies labelled with fluorescent probes that are specific for endothelial antigens. The number of endothelial cells is then counted at the flowcytometry based on the number of cells with positive fluorescence (132). While this technique is relatively simple and enables a rapid assessment of the number of CECs, the use of different antigens to identify endothelial cells by different research groups and the lack of an international agreement on the protocols makes impossible its application in clinical practice at present. The immunobeads assay, by contrast, is recognised as the most accurate method to isolate and count CECs in peripheral blood (133). Antibodies specific for specific endothelial antigens labelled with magnetic beads are incubated with the whole blood. After this incubation, endothelial cells are isolated using a magnet. These cells can be further stained with other antibodies specific for endothelial cells and are then counted at a fluorescent microscope.

In contrast, assessment of the number and phenotype of EMPs and EPCs in peripheral blood by flowcytometry requires experience, making this measure feasible only in trained laboratories. The use of fluorescent-labelled antibodies is necessary to characterize the surface antigens of EMPs and EPCs, defining not only their numbers but also their phenotypes (including origins, differentiation or activation).

### EVIDENCE OF ENDOTHELIAL DYSFUNCTION/DAMAGE IN HYPERTENSION

Homogeneous literature convincingly demonstrates the presence of endothelial damage in the hypertensive patient (14,118). Early signs of this damage manifest in the

form of endothelial dysfunction. An increased vascular wall breakdown of NO is identified from the earliest stages of hypertension in humans as well as in experimental animals. This is related to an increased production of ROS in the vascular wall of hypertensive patients (118). Various enzymatic and non-enzymatic sources of ROS have been described to be activated in endothelial cells, smooth muscle cells and inflammatory cells within the arterial wall of hypertensive patients, including nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, cyclooxygenase, xanthine oxidase and uncoupled eNOS (134–136). Recent evidence suggests that mitochondria could also contribute to the increased levels of vascular wall ROS detected in hypertension (137). This could induce oxidative DNA damage in the mitochondria of endothelial and smooth muscle cells (138) that may affect the synthesis of components of the respiratory chain, leading to a further increase in mtROS production, ultimately initiating a vicious cycle. Interestingly, mutations in mitochondrial DNA are also associated with increased risk of hypertension (139–141), suggesting that these alterations might precede and be in the causal pathway for the disease initiation and evolution.

Although FMD and the microvascular techniques showed their ability to capture the presence of early endothelial dysfunction in different vascular districts of hypertensive patients (14,98,118,142–147), the opportunity to use endothelial agonists or antagonists to manipulate endothelial function in the forearm plethysmography and the micromyography has enabled more complex studies that not only confirmed the presence of endothelial damage in hypertension, but also clarified the mechanisms underlying the development of this damage. For example, using these techniques it was possible to confirm that, while NO release has a strong influence on the vasodilator response to of acetylcholine or bradykinin in the forearm of healthy subjects (12,148,149), in hypertensive patients the response to these agonists is not only blunted but also partially resistant to the inhibition of the eNOS by L-NAME (118,143,150). This suggested that other endothelial-derived hyperpolarising factors could account for the endothelial response in hypertension (12). Further microvascular studies have confirmed that the reduced NO availability detected in hypertensive patients was attributable to an excessive oxidative stress production, which causes NO breakdown (118). In the forearm microcirculation it was suggested that the cyclooxygenase pathway actively interferes with NO availability and represents a source of ROS (150). More recent experiments conducted in isolated small vessels from hypertensive patients confirmed this finding and evidenced that cyclooxygenase-2 could represent the main isoform able to act as a source of oxidative stress (136). In such a scenario, cytochrome P-450 2C9–derived EDHF might act as a partial compensatory mechanism to sustain endothelium-dependent vasodilation (27).

Increased levels of E-selectin, VCAM and ICAM have been described by multiple research groups in patients with hypertension (151–153). This increase seems to be present from the earliest stage of the disease (153), suggesting that these markers might be sensitive enough to detect the earliest stages of endothelial damage in hypertension. However, a study conducted to assess the relationship between E-selectin levels and endothelium-dependent vasodilation showed that, despite

the presence of increased E-selectin concentrations and reduced endothelium-dependent vasodilation in hypertensive patients as compared to normotensive controls, no significant correlation among the two endothelial parameters was found (154). These data suggest that, at least in patients with essential hypertension, levels of E-selectin are mostly related to structural, rather than functional (endothelial), vascular changes.

The different methods used to count the CECs have generated conflicting results regarding their ability to mark the endothelial damage in patients with hypertension. While some studies found a higher number of CECs in the peripheral circulation of patients with hypertension compared to normotensive subjects (155,156), these results could not be replicated by other reports (157).

The need for more standardised protocols which require extensive operator training has produced more convincing evidence about the capacity of EMPs to characterise the severity of endothelial damage in hypertension. In the Framingham Heart Study, the number of EMPs was higher in patients with hypertension than normotensive subjects. Another study by Preston et al. reported a significant increase in the amount of endothelial and platelet microparticles in patients with severe arterial hypertension, and showed strong relationships between the amount of circulating EMPs and the level of both systolic and diastolic blood pressures (60). The hypothesis that EMPs can be used as circulating markers for endothelial injury following the hemodynamic changes due to hypertension is further supported by studies in which increased levels of circulating EMPs had been found in patients with pre-eclampsia (58,59) and in patients with pulmonary hypertension (158–160). Importantly, EMPs have been linked also to the decline of the glomerular filtration rate (161) and the degree of increased arterial stiffness (162) in hypertensive patients, suggesting they could be used to monitor the severity of the generalised endotheliopathy leading to the progression of micro- and macro-vascular complications in arterial hypertension.

To understand the relationship between EPCs and hypertension, it is important to consider that not only the number of circulating cells but also their function (in terms of repair capacity and survival) might provide important clues on the evolution of the disease and its impact on the endothelial biology. Indeed, current evidence suggests that functional decline of EPCs occurs earlier and more commonly than reductions in EPC quantity in patients with essential hypertension (163–166). Function of EPCs is dependent on NO availability and levels of oxidative stress (167). Thus the early development of endothelial damage in the form of endothelial dysfunction might explain the altered function of the EPC in patients with arterial hypertension. Increased levels of oxidative stress are also able to reduce EPC lifespan, stimulating further recruitment of EPCs from the bone marrow to repair this early endothelial damage. However, with progression of the damage associated with advanced hypertension and progressive exhaustion of the bone marrow regenerative capacities, the number of EPCs might progressively decline, directly contributing to further progression of the damage. Indeed, the quantitative and functional declines of EPCs become more pronounced in the advanced stages of hypertension (i.e. in patients with resistant hypertension, increased incidence of adverse vascular events and end-organ damage)



(168–172). While this hypothetical sequence of events might resume most of the current evidence exploring the relationship between EPC and hypertension, accumulating data suggest that the association between EPCs, hypertension and cardiovascular outcomes is far more complicated than we had previously thought. Different types of EPCs may have distinct pathogenetic roles and may be affected differently in pathways contributing to hypertension (e.g. late EPCs undergo more significant declines in proliferative activity than other types of EPCs) (168,173), suggesting that there exist much more complex regulatory mechanisms that mediate the hypertension – EPC relationship and require further investigation.

Despite this large body of evidence confirming the presence of endothelial damage in hypertension, whether endothelial damage is a cause or effect of hypertension remains a matter of debate. In the Young Finns Study, elevated blood pressure recorded in teenagers was predictive of impaired FMD after 21 years of follow-up (174). Similar results were obtained by Jurva et al., who showed that acute, large increases in blood pressure acutely impair FMD in young adults who were otherwise healthy (175). In the Multi-Ethnic Study of Atherosclerosis (MESA), Shimbo and colleagues found that impaired FMD was not a significant independent predictor of the future development of hypertension (176). This evidence supports the hypothesis that an altered endothelial biology is unlikely to cause, but rather be a consequence of, arterial hypertension. However, other data suggest the presence of a relationship in the opposite direction. For example, inhibition of the eNOS results in hypertension in humans (177) and, studying a cohort study of postmenopausal women, Rossi et al. showed that normotensive women with impaired endothelial function have a nearly sixfold increased risk of developing hypertension (178). Data in support of endothelial damage/dysfunction preceding the development of hypertension also come from familial studies. Taddei et al. showed that normotensive offspring of hypertensive patients had significantly impaired response to acetylcholine in comparison to normotensive offspring of normotensive patients, due to a defect in the L-arginine–NO pathway (179), suggesting that genetic factors controlling endothelial function can anticipate the development of hypertension. Thus, current evidence does not enable drawing a definitive conclusion on the cause–effect relationship between endothelial damage and hypertension, with some authors suggesting a ‘vicious circle’ hypothesis; that is, a bidirectional relationship (180).

## CONCLUSION

Robust evidence confirms the presence of an altered endothelial biology leading to cellular damage in hypertension. This is detectable from the earliest stages of the diseases, in patients with and without previous cardiovascular events as well as in subjects with and without end-organ damage. As hypertension remains the leading cause of morbidity and mortality worldwide, further studies are needed to clarify the cause–effect relationship between endothelial damage and hypertension, in the attempt to identify novel therapeutic targets that could be used to prevent the disease and/or its complications.

## REFERENCES

1. Yusuf S, Rangarajan S, Teo K et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med* 2014; 371(9): 818–827.
2. Vita JA, Keaney JF, Jr. Endothelial function: A barometer for cardiovascular risk? *Circulation* 2002; 106(6): 640–642.
3. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980; 288(5789): 373–376.
4. Furchgott RF, Vanhoutte PM. Endothelium-derived relaxing and contracting factors. *FASEB J* 1989; 3(9): 2007–2018.
5. Loscalzo J. The identification of nitric oxide as endothelium-derived relaxing factor. *Circ Res* 2013; 113(2): 100–103.
6. Moncada S. Nitric oxide in the vasculature: Physiology and pathophysiology. *Ann N Y Acad Sci* 1997; 811: 60–67, discussion 67–69.
7. Vanhoutte PM. How we learned to say NO. *Arterioscler Thromb Vasc Biol* 2009; 29(8): 1156–1160.
8. Ignarro LJ. Biosynthesis and metabolism of endothelium-derived nitric oxide. *Annu Rev Pharmacol Toxicol* 1990; 30: 535–560.
9. Corson MA, James NL, Latta SE et al. Phosphorylation of endothelial nitric oxide synthase in response to fluid shear stress. *Circ Res* 1996; 79(5): 984–991.
10. Govers R, Rabelink TJ. Cellular regulation of endothelial nitric oxide synthase. *Am J Physiol Renal Physiol* 2001; 280(2): F193–F206.
11. Cohen RA, Vanhoutte PM. Endothelium-dependent hyperpolarization. Beyond nitric oxide and cyclic GMP. *Circulation* 1995; 92(11): 3337–3349.
12. Taddei S, Ghiadoni L, Virdis A et al. Vasodilation to bradykinin is mediated by an ouabain-sensitive pathway as a compensatory mechanism for impaired nitric oxide availability in essential hypertensive patients. *Circulation* 1999; 100(13): 1400–1405.
13. Endemann DH, Schiffrin EL. Endothelial dysfunction. *J Am Soc Nephrol* 2004; 15(8): 1983–1992.
14. Panza JA, Quyyumi AA, Brush JE, Jr, Epstein SE. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. *N Engl J Med* 1990; 323(1): 22–27.
15. Orlandi M, Suvan J, Petrie A et al. Association between periodontal disease and its treatment, flow-mediated dilatation and carotid intima-media thickness: A systematic review and meta-analysis. *Atherosclerosis* 2014; 236(1): 39–46.
16. Luscher TF, Barton M. Biology of the endothelium. *Clin Cardiol* 1997; 20(11): II-3–II-10.
17. Munzel T, Gori T, Bruno RM, Taddei S. Is oxidative stress a therapeutic target in cardiovascular disease? *Eur Heart J* 2010; 31(22): 2741–2748.
18. Forstermann U, Munzel T. Endothelial nitric oxide synthase in vascular disease: From marvel to menace. *Circulation* 2006; 113(13): 1708–1714.
19. Murphy MP. How mitochondria produce reactive oxygen species. *Biochem J* 2009; 417(1): 1–13.
20. Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. *Nature* 2011; 469(7329): 221–225.
21. Widlansky ME, Gutterman DD. Regulation of endothelial function by mitochondrial reactive oxygen species. *Antioxid Redox Signal* 2011; 15(6): 1517–1530.
22. Sun N, Youle RJ, Finkel T. The mitochondrial basis of aging. *Mol Cell* 2016; 61(5): 654–666.
23. Kizhakekuttu TJ, Wang J, Dharmashankar K et al. Adverse alterations in mitochondrial function contribute to type 2 diabetes mellitus-related endothelial dysfunction in humans. *Arterioscler Thromb Vasc Biol* 2012; 32(10): 2531–2539.
24. Widlansky ME, Wang J, Shenouda SM et al. Altered mitochondrial membrane potential, mass, and morphology in the mononuclear cells of humans with type 2 diabetes. *Transl Res* 2010; 156(1): 15–25.
25. Gioscia-Ryan RA, LaRocca TJ, Sindler AL et al. Mitochondria-targeted antioxidant (MitoQ) ameliorates age-related arterial endothelial dysfunction in mice. *J Physiol* 2014; 592(12): 2549–2561.
26. Park SY, Kwon OS, Andtbacka RHI et al. Age-related endothelial dysfunction in human skeletal muscle feed arteries: The role of free radicals derived from mitochondria in the vasculature. *Acta Physiologica* 2017; 222(1).
27. Taddei S, Versari D, Cipriano A et al. Identification of a cytochrome P450 2C9-derived endothelium-derived hyperpolarizing factor in essential hypertensive patients. *J Am Coll Cardiol* 2006; 48(3): 508–515.

28. Taddei S, Virdis A, Ghiadoni L et al. Vasoconstriction to endogenous endothelin-1 is increased in the peripheral circulation of patients with essential hypertension. *Circulation* 1999; 100(16): 1680–1683.
29. Bevilacqua MP, Nelson RM. Endothelial-leukocyte adhesion molecules in inflammation and metastasis. *Thromb Haemostasis* 1993; 70(1): 152–154.
30. Carlos TM, Harlan JM. Leukocyte-endothelial adhesion molecules. *Blood* 1994; 84(7): 2068–2101.
31. Frijns CJ, Kappelle LJ, van Gijn J et al. Soluble adhesion molecules reflect endothelial cell activation in ischemic stroke and in carotid atherosclerosis. *Stroke* 1997; 28(11): 2214–2218.
32. Baker CS, Hall RJ, Evans TJ et al. Cyclooxygenase-2 is widely expressed in atherosclerotic lesions affecting native and transplanted human coronary arteries and colocalizes with inducible nitric oxide synthase and nitrotyrosine particularly in macrophages. *Arterioscler Thromb Vasc Biol* 1999; 19(3): 646–655.
33. Myatt L, Rosenfield RB, Eis AL et al. Nitrotyrosine residues in placenta. Evidence of peroxynitrite formation and action. *Hypertension* 1996; 28(3): 488–493.
34. Quijano C, Castro L, Peluffo G et al. Enhanced mitochondrial superoxide in hyperglycemic endothelial cells: Direct measurements and formation of hydrogen peroxide and peroxynitrite. *Am J Physiol Heart Circ Physiol* 2007; 293(6): H3404–H3414.
35. Jablonski KL, Gates PE, Pierce GL, Seals DR. Low dietary sodium intake is associated with enhanced vascular endothelial function in middle-aged and older adults with elevated systolic blood pressure. *Ther Adv Cardiovasc Dis* 2009; 3(5): 347–356.
36. Griending KK, Sorescu D, Ushio-Fukai M. NAD(P)H oxidase: Role in cardiovascular biology and disease. *Circ Res* 2000; 86(5): 494–501.
37. Price DT, Vita JA, Keaney JE, Jr. Redox control of vascular nitric oxide bioavailability. *Antioxid Redox Signal* 2000; 2(4): 919–935.
38. Durrant JR, Seals DR, Connell ML et al. Voluntary wheel running restores endothelial function in conduit arteries of old mice: Direct evidence for reduced oxidative stress, increased superoxide dismutase activity and down-regulation of NADPH oxidase. *J Physiol* 2009; 587(Pt 13): 3271–3285.
39. Lesniewski LA, Connell ML, Durrant JR et al. B6D2F1 Mice are a suitable model of oxidative stress-mediated impaired endothelium-dependent dilation with aging. *J Gerontol A Biol Sci Med Sci* 2009; 64(1): 9–20.
40. Miller SJ, Watson WC, Kerr KA et al. Development of progressive aortic vasculopathy in a rat model of aging. *Am J Physiol Heart Circ Physiol* 2007; 293(5): H2634–H2643.
41. Donato AJ, Eskurza I, Silver AE et al. Direct evidence of endothelial oxidative stress with aging in humans: Relation to impaired endothelium-dependent dilation and upregulation of nuclear factor-kappaB. *Circ Res* 2007; 100(11): 1659–1666.
42. Gong X, Ma Y, Ruan Y, Fu G, Wu S. Long-term atorvastatin improves age-related endothelial dysfunction by ameliorating oxidative stress and normalizing eNOS/iNOS imbalance in rat aorta. *Exp Gerontol* 2014; 52: 9–17.
43. Oelze M, Kroller-Schon S, Steven S et al. Glutathione peroxidase-1 deficiency potentiates dysregulatory modifications of endothelial nitric oxide synthase and vascular dysfunction in aging. *Hypertension* 2014; 63(2): 390–396.
44. Uddin M, Yang H, Shi M et al. Elevation of oxidative stress in the aorta of genetically hypertensive mice. *Mech Ageing Dev* 2003; 124(7): 811–817.
45. Ungvari Z, Bailey-Downs L, Gautam T et al. Age-associated vascular oxidative stress, Nrf2 dysfunction, and NF- $\kappa$ B activation in the nonhuman primate *Macaca mulatta*. *J Gerontol A Biol Sci Med Sci* 2011; 66(8): 866–875.
46. Mallat Z, Benamer H, Hugel B et al. Elevated levels of shed membrane microparticles with procoagulant potential in the peripheral circulating blood of patients with acute coronary syndromes. *Circulation* 2000; 101(8): 841–843.
47. Woywodt A, Bahlmann FH, De Groot K et al. Circulating endothelial cells: Life, death, detachment and repair of the endothelial cell layer. *Nephrol Dial Transplant* 2002; 17(10): 1728–1730.
48. VanWijk MJ, VanBavel E, Sturk A, Nieuwland R. Microparticles in cardiovascular diseases. *Cardiovasc Res* 2003; 59(2): 277–287.
49. Schiro A, Wilkinson FL, Weston R, Smyth JV, Serracino-Inglott F, Alexander MY. Endothelial microparticles as conveyors of information in atherosclerotic disease. *Atherosclerosis* 2014; 234(2): 295–302.
50. Leroyer AS, Ebrahimian TG, Cochain C et al. Microparticles from ischemic muscle promotes postnatal vasculogenesis. *Circulation* 2009; 119(21): 2808–2817.
51. Combes V, Simon AC, Grau GE et al. In vitro generation of endothelial microparticles and possible prothrombotic activity in patients with lupus anticoagulant. *J Clin Invest* 1999; 104(1): 93–102.
52. Szotowski B, Antoniak S, Goldin-Lang P et al. Antioxidative treatment inhibits the release of thrombogenic tissue factor from irradiation- and cytokine-induced endothelial cells. *Cardiovasc Res* 2007; 73(4): 806–812.
53. Brodsky SV, Malinowski K, Golightly M et al. Plasminogen activator inhibitor-1 promotes formation of endothelial microparticles with procoagulant potential. *Circulation* 2002; 106(18): 2372–2378.
54. Sapet C, Simoncini S, Llorid B et al. Thrombin-induced endothelial microparticle generation: Identification of a novel pathway involving ROCK-II activation by caspase-2. *Blood* 2006; 108(6): 1868–1876.
55. Simak J, Holada K, Vostal JG. Release of annexin V-binding membrane microparticles from cultured human umbilical vein endothelial cells after treatment with camptothecin. *BMC Cell Biol* 2002; 3: 11.
56. Wang JM, Wang Y, Huang JY et al. C-Reactive protein-induced endothelial microparticle generation in HUVECs is related to BH4-dependent NO formation. *J Vasc Res* 2007; 44(3): 241–248.
57. Faure V, Dou L, Sabatier F et al. Elevation of circulating endothelial microparticles in patients with chronic renal failure. *J Thromb Haemost* 2006; 4(3): 566–573.
58. Gonzalez-Quintero VH et al. Elevated plasma endothelial microparticles: Preeclampsia versus gestational hypertension. *Am J Obstet Gynecol* 2004; 191(4): 1418–1424.
59. Marques FK, Campos FM, Sousa LP et al. Association of microparticles and preeclampsia. *Mol Biol Rep* 2013; 40(7): 4553–4559.
60. Preston RA, Jy W, Jimenez JJ et al. Effects of severe hypertension on endothelial and platelet microparticles. *Hypertension* 2003; 41(2): 211–217.
61. Bernal-Mizrachi L, Jy W, Jimenez JJ et al. High levels of circulating endothelial microparticles in patients with acute coronary syndromes. *Am Heart J* 2003; 145(6): 962–970.
62. Simak J, Gelderman MP, Yu H et al. Circulating endothelial microparticles in acute ischemic stroke: A link to severity, lesion volume and outcome. *J Thromb Haemost* 2006; 4(6): 1296–1302.
63. Amabile N, Guerin AP, Leroyer A et al. Circulating endothelial microparticles are associated with vascular dysfunction in patients with end-stage renal failure. *J Am Soc Nephrol* 2005; 16(11): 3381–3388.
64. Esposito K, Ciotola M, Schisano B et al. Endothelial microparticles correlate with endothelial dysfunction in obese women. *J Clin Endocrinol Metab* 2006; 91(9): 3676–3679.
65. Koga H, Sugiyama S, Kugiyama K et al. Elevated levels of VE-cadherin-positive endothelial microparticles in patients with type 2 diabetes mellitus and coronary artery disease. *J Am Coll Cardiol* 2005; 45(10): 1622–1630.
66. Werner N, Wassmann S, Ahlers P et al. Circulating CD31+/annexin V+ apoptotic microparticles correlate with coronary endothelial function in patients with coronary artery disease. *Arterioscler Thromb Vasc Biol* 2006; 26(1): 112–116.
67. Markiewicz M, Richard E, Marks N, Ludwicka-Bradley A. Impact of endothelial microparticles on coagulation, inflammation, and angiogenesis in age-related vascular diseases. *J Aging Res* 2013; 2013: 734509.
68. Dignat-George F, Boulanger CM. The many faces of endothelial microparticles. *Arterioscler Thromb Vasc Biol* 2011; 31(1): 27–33.
69. Blann AD, Woywodt A, Bertolini F et al. Circulating endothelial cells. Biomarker of vascular disease. *Thromb Haemost* 2005; 93(2): 228–235.
70. Bouvier CAG, E, Cintron JR, Bernhardt B, Spaet TH. Circulating endothelium as an indication of vascular injury. *Thromb Diath Haemorrh* 1970; 40: 1.
71. Re F, Zanetti A, Sironi M, Polentarutti N et al. Inhibition of anchorage-dependent cell spreading triggers apoptosis in cultured human endothelial cells. *J Cell Biol* 1994; 127(2): 537–546.
72. Ruegg C, Yilmaz A, Bieler G et al. Evidence for the involvement of endothelial cell integrin  $\alpha$ V $\beta$ 3 in the disruption of the tumor vasculature induced by TNF and IFN- $\gamma$ . *Nat Med* 1998; 4(4): 408–414.
73. Boos CJ, Lip GY, Blann AD. Circulating endothelial cells in cardiovascular disease. *J Am Coll Cardiol* 2006; 48(8): 1538–1547.
74. McClung JA, Naseer N, Saleem M et al. Circulating endothelial cells are elevated in patients with type 2 diabetes mellitus independently of HbA(1)c. *Diabetologia* 2005; 48(2): 345–350.



75. Woywodt A, Streiber F, de Groot K et al. Circulating endothelial cells as markers for ANCA-associated small-vessel vasculitis. *Lancet* 2003; 361(9353): 206–210.
76. Strijbos MH, Landburg PP, Nur E et al. Circulating endothelial cells: A potential parameter of organ damage in sickle cell anemia? *Blood Cells Mol Dis* 2009; 43(1): 63–67.
77. Boos CJ, Mayr FB, Lip GY, Jilma B. Endotoxemia enhances circulating endothelial cells in humans. *J Thromb Haemost* 2006; 4(11): 2509–2511.
78. Erdbruegger U, Dhaygude A, Haubitz M, Woywodt A. Circulating endothelial cells: Markers and mediators of vascular damage. *Curr Stem Cell Res Ther* 2010; 5(4): 294–302.
79. Bertolini F, Shaked Y, Mancuso P, Kerbel RS. The multifaceted circulating endothelial cell in cancer: Towards marker and target identification. *Nat Rev Cancer* 2006; 6(11): 835–845.
80. Kraan J, Strijbos MH, Sieuwerts AM et al. A new approach for rapid and reliable enumeration of circulating endothelial cells in patients. *J Thromb Haemost* 2012; 10(5): 931–939.
81. Widemann A, Sabatier F, Arnaud L et al. CD146-based immunomagnetic enrichment followed by multiparameter flow cytometry: A new approach to counting circulating endothelial cells. *J Thromb Haemost* 2008; 6(5): 869–876.
82. Goon PK, Boos CJ, Stonelake PS, Blann AD, Lip GY. Detection and quantification of mature circulating endothelial cells using flow cytometry and immunomagnetic beads: A methodological comparison. *Thromb Haemostasis* 2006; 96(1): 45–52.
83. Martin-Padura IB F. Circulating endothelial cells as biomarkers for angiogenesis in tumor progression. *Front Biosci (Schol Ed)* 2009; 1: 15.
84. Op den Buijs J, Musters M, Verrips T et al. Mathematical modeling of vascular endothelial layer maintenance: The role of endothelial cell division, progenitor cell homing, and telomere shortening. *Am J Physiol Heart Circ Physiol* 2004; 287(6): H2651–H2658.
85. Asahara T, Murohara T, Sullivan A et al. Isolation of putative progenitor endothelial cells for angiogenesis. *Science* 1997; 275(5302): 964–967.
86. Chong MS, Ng WK, Chan JK. Concise review: Endothelial progenitor cells in regenerative medicine: Applications and challenges. *Stem Cells Transl Med* 2016; 5(4): 530–538.
87. Ingram DA, Mead LE, Tanaka H et al. Identification of a novel hierarchy of endothelial progenitor cells using human peripheral and umbilical cord blood. *Blood* 2004; 104(9): 2752–2760.
88. Melero-Martin JM, Khan ZA, Picard A et al. In vivo vasculogenic potential of human blood-derived endothelial progenitor cells. *Blood* 2007; 109(11): 4761–4768.
89. Wang QR, Wang BH, Zhu WB et al. An *in vitro* study of differentiation of hematopoietic cells to endothelial cells. *Bone Marrow Res* 2011; 2011: 846096.
90. Aicher A, Heeschen C, Mildner-Rihm C et al. Essential role of endothelial nitric oxide synthase for mobilization of stem and progenitor cells. *Nat Med* 2003; 9(11): 1370–1376.
91. Hill JM, Zalos G, Halcox JP et al. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. *N Engl J Med* 2003; 348(7): 593–600.
92. Gossel M, Modder UI, Gulati R et al. Coronary endothelial dysfunction in humans is associated with coronary retention of osteogenic endothelial progenitor cells. *Eur Heart J* 2010; 31(23): 2909–2914.
93. Werner N, Wassmann S, Ahlers P et al. Endothelial progenitor cells correlate with endothelial function in patients with coronary artery disease. *Basic Res Cardiol* 2007; 102(6): 565–571.
94. Altabas V, Altabas K, Kirigin L. Endothelial progenitor cells (EPCs) in ageing and age-related diseases: How currently available treatment modalities affect EPC biology, atherosclerosis, and cardiovascular outcomes. *Mech Ageing Dev* 2016; 159: 49–62.
95. Flammer AJ, Anderson T, Celermajer DS et al. The assessment of endothelial function: From research into clinical practice. *Circulation* 2012; 126(6): 753–767.
96. Ludmer PL, Selwyn AP, Shook TL et al. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. *N Engl J Med* 1986; 315(17): 1046–1051.
97. Egashira K, Suzuki S, Hirooka Y et al. Impaired endothelium-dependent vasodilation of large epicardial and resistance coronary arteries in patients with essential hypertension. Different responses to acetylcholine and substance P. *Hypertension* 1995; 25(2): 201–206.
98. Quyyumi AA, Cannon RO, 3rd, Panza JA et al. Endothelial dysfunction in patients with chest pain and normal coronary arteries. *Circulation* 1992; 86(6): 1864–1871.
99. Treasure CB, Klein JL, Vita JA et al. Hypertension and left ventricular hypertrophy are associated with impaired endothelium-mediated relaxation in human coronary resistance vessels. *Circulation* 1993; 87(1): 86–93.
100. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation* 2000; 101(16): 1899–1906.
101. Frielingsdorf J, Kaufmann P, Seiler C et al. Abnormal coronary vasomotion in hypertension: Role of coronary artery disease. *J Am Coll Cardiol* 1996; 28(4): 935–941.
102. Nitenberg A, Antony I, Aptekar E et al. Impairment of flow-dependent coronary dilation in hypertensive patients. Demonstration by cold pressor test induced flow velocity increase. *Am J Hypertens* 1995; 8(5 Pt 2): 13S–18S.
103. Zeiher AM, Drexler H, Wollschläger H et al. Coronary vasomotion in response to sympathetic stimulation in humans: Importance of the functional integrity of the endothelium. *J Am Coll Cardiol* 1989; 14(5): 1181–1190.
104. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med* 2007; 356(8): 830–840.
105. Goodhart DM, Anderson TJ. Role of nitric oxide in coronary arterial vasomotion and the influence of coronary atherosclerosis and its risks. *Am J Cardiol* 1998; 82(9): 1034–1039.
106. Celermajer DS, Sorensen KE, Gooch VM et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 1992; 340(8828): 1111–1115.
107. Joannides R, Haefeli WE, Linder L et al. Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries *in vivo*. *Circulation* 1995; 91(5): 1314–1319.
108. Charakida M, Masi S, Luscher TF et al. Assessment of atherosclerosis: The role of flow-mediated dilatation. *Eur Heart J* 2010; 31(23): 2854–2861.
109. Donald AE, Halcox JP, Charakida M et al. Methodological approaches to optimize reproducibility and power in clinical studies of flow-mediated dilation. *J Am Coll Cardiol* 2008; 51(20): 1959–1964.
110. Ghiadoni L, Donald AE, Cropley M et al. Mental stress induces transient endothelial dysfunction in humans. *Circulation* 2000; 102(20): 2473–2478.
111. Charakida M, de Groot E, Loukogeorgakis SP et al. Variability and reproducibility of flow-mediated dilatation in a multicentre clinical trial. *Eur Heart J* 2013; 34(45): 3501–3507.
112. Ghiadoni L, Fatta F, Salvetti M et al. Assessment of flow-mediated dilation reproducibility: A nationwide multicenter study. *J Hypertens* 2012; 30(7): 1399–1405.
113. Kuvin JT, Patel AR, Sliney KA et al. Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. *Am Heart J* 2003; 146(1): 168–174.
114. Hamburg NM, Keyes MJ, Larson MG et al. Cross-sectional relations of digital vascular function to cardiovascular risk factors in the Framingham Heart Study. *Circulation* 2008; 117(19): 2467–2474.
115. Nohria A, Gerhard-Herman M, Creager MA et al. Role of nitric oxide in the regulation of digital pulse volume amplitude in humans. *J Appl Physiol* 2006; 101(2): 545–548.
116. Schnabel RB, Schulz A, Wild PS et al. Noninvasive vascular function measurement in the community: Cross-sectional relations and comparison of methods. *Circ Cardiovasc Imaging* 2011; 4(4): 371–380.
117. Wilkinson IB, Webb DJ. Venous occlusion plethysmography in cardiovascular research: Methodology and clinical applications. *Br J Clin Pharmacol* 2001; 52(6): 631–646.
118. Taddei S, Virdis A, Ghiadoni L et al. Vitamin C improves endothelium-dependent vasodilation by restoring nitric oxide activity in essential hypertension. *Circulation* 1998; 97(22): 2222–2229.
119. Ensink D, Wolpers HG, Zipfel J, Hellige G. The reliability of venous capacity and blood flow determination by plethysmograph. In: Jagenau AHM (ed). *Non-Invasive Methods on Cardiovascular Haemodynamics*. Amsterdam: Elsevier; 1981: 215–226.
120. Dahn I, Hallbook T. Simultaneous blood flow measurements by water and strain gauge plethysmography. *Scand J Clin Lab Invest* 1970; 25(4): 419–428.
121. Heitzer T, Schlinzig T, Krohn K et al. Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. *Circulation* 2001; 104(22): 2673–2678.
122. Virdis A, Ghiadoni L, Qasem AA et al. Effect of aliskiren treatment on endothelium-dependent vasodilation and aortic stiffness in essential hypertensive patients. *Eur Heart J* 2012; 33(12): 1530–1538.

123. Mulvany MJ, Halpern W. Contractile properties of small arterial resistance vessels in spontaneously hypertensive and normotensive rats. *Circ Res* 1977; 41(1): 19–26.
124. Virdis A, Savoia C, Grassi G et al. Evaluation of microvascular structure in humans: A 'state-of-the-art' document of the Working Group on Macrovascular and Microvascular Alterations of the Italian Society of Arterial Hypertension. *J Hypertens* 2014; 32(11): 2120–2129, discussion 2129.
125. Vecchione C, Carnevale D, Di Pardo A et al. Pressure-induced vascular oxidative stress is mediated through activation of integrin-linked kinase 1/betaPIX/Rac-1 pathway. *Hypertension* 2009; 54(5): 1028–1034.
126. Vecchione C, Frati A, Di Pardo A et al. Tumor necrosis factor- $\alpha$  mediates hemolysis-induced vasoconstriction and the cerebral vasospasm evoked by subarachnoid hemorrhage. *Hypertension* 2009; 54(1): 150–156.
127. Constans J, Conri C. Circulating markers of endothelial function in cardiovascular disease. *Clin Chim Acta* 2006; 368(1–2): 33–47.
128. Gimbrone MA Jr, Cybulsky MI, Kume N et al. Vascular endothelium. An integrator of pathophysiological stimuli in atherogenesis. *Ann N Y Acad Sci* 1995; 748: 122–131, discussion 131–122.
129. Ishii H, Uchiyama H, Kazama M. Soluble thrombomodulin antigen in conditioned medium is increased by damage of endothelial cells. *Thromb Haemostasis* 1991; 65(5): 618–623.
130. Vlot AJ, Koppelman SJ, Bouma BN, Sixma JJ. Factor VIII and von Willebrand factor. *Thromb Haemostasis* 1998; 79(3): 456–465.
131. Lip GY, Blann A. von Willebrand factor: A marker of endothelial dysfunction in vascular disorders? *Cardiovasc Res* 1997; 34(2): 255–265.
132. Khan SS, Solomon MA, McCoy JP, Jr. Detection of circulating endothelial cells and endothelial progenitor cells by flow cytometry. *Cytometry B Clin Cytom* 2005; 64(1): 1–8.
133. Woywodt A, Blann AD, Kirsch T et al. Isolation and enumeration of circulating endothelial cells by immunomagnetic isolation: Proposal of a definition and a consensus protocol. *J Thromb Haemost* 2006; 4(3): 671–677.
134. Li Q, Youn JY, Cai H. Mechanisms and consequences of endothelial nitric oxide synthase dysfunction in hypertension. *J Hypertens* 2015; 33(6): 1128–1136.
135. Schulz E, Gori T, Munzel T. Oxidative stress and endothelial dysfunction in hypertension. *Hypertens Res* 2011; 34(6): 665–673.
136. Virdis A, Bacca A, Colucci R et al. Endothelial dysfunction in small arteries of essential hypertensive patients: Role of cyclooxygenase-2 in oxidative stress generation. *Hypertension* 2013; 62(2): 337–344.
137. Dikalov SI, Dikalova AE. Contribution of mitochondrial oxidative stress to hypertension. *Curr Opin Nephrol Hypertens* 2016; 25(2): 73–80.
138. Ballinger SW, Patterson C, Yan CN et al. Hydrogen peroxide- and peroxynitrite-induced mitochondrial DNA damage and dysfunction in vascular endothelial and smooth muscle cells. *Circ Res* 2000; 86(9): 960–966.
139. Elango S, Govindaraj P, Vishwanadha VP et al. Analysis of mitochondrial genome revealed a rare 50 bp deletion and substitutions in a family with hypertension. *Mitochondrion* 2011; 11(6): 878–885.
140. Rea IM, McNerlan SE, Archbold GP et al. Mitochondrial J haplogroup is associated with lower blood pressure and anti-oxidant status: Findings in octo/nonagenarians from the BELFAST Study. *Age* 2013; 35(4): 1445–1456.
141. Teng L, Zheng J, Leng J, Ding Y. Clinical and molecular characterization of a Han Chinese family with high penetrance of essential hypertension. *Mitochondrial DNA* 2012; 23(6): 461–465.
142. Ghiadoni L, Magagna A, Versari D et al. Different effect of antihypertensive drugs on conduit artery endothelial function. *Hypertension* 2003; 41(6): 1281–1286.
143. Panza JA, Casino PR, Kilcoyne CM, Quyyumi AA. Role of endothelium-derived nitric oxide in the abnormal endothelium-dependent vascular relaxation of patients with essential hypertension. *Circulation* 1993; 87(5): 1468–1474.
144. Taddei S, Virdis A, Mattei P et al. Aging and endothelial function in normotensive subjects and patients with essential hypertension. *Circulation* 1995; 91(7): 1981–1987.
145. Taddei S, Virdis A, Mattei P, Salvetti A. Vasodilation to acetylcholine in primary and secondary forms of human hypertension. *Hypertension* 1993; 21(6 Pt 2): 929–933.
146. Treasure CB, Manoukian SV, Klein JL et al. Epicardial coronary artery responses to acetylcholine are impaired in hypertensive patients. *Circ Res* 1992; 71(4): 776–781.
147. Virdis A, Ghiadoni L, Cardinal H et al. Mechanisms responsible for endothelial dysfunction induced by fasting hyperhomocystinemia in normotensive subjects and patients with essential hypertension. *J Am Coll Cardiol* 2001; 38(4): 1106–1115.
148. John S, Schmieder RE. Impaired endothelial function in arterial hypertension and hypercholesterolemia: Potential mechanisms and differences. *J Hypertens* 2000; 18(4): 363–374.
149. Taddei S, Virdis A, Mattei P et al. Hypertension causes premature aging of endothelial function in humans. *Hypertension* 1997; 29(3): 736–743.
150. Taddei S, Virdis A, Ghiadoni L et al. Cyclooxygenase inhibition restores nitric oxide activity in essential hypertension. *Hypertension* 1997; 29(1 Pt 2): 274–279.
151. Blann AD, Tse W, Maxwell SJ, Waite MA. Increased levels of the soluble adhesion molecule E-selectin in essential hypertension. *J Hypertens* 1994; 12(8): 925–928.
152. DeSouza CA, Dengel DR, Macko RF et al. Elevated levels of circulating cell adhesion molecules in uncomplicated essential hypertension. *Am J Hypertens* 1997; 10(12 Pt 1): 1335–1341.
153. Goonasekera CDA. Vascular endothelial cell activation associated with increased plasma asymmetric dimethyl arginine in children and young adults with hypertension: A basis for atheroma? *Blood Press* 2000; 9(1): 16–21.
154. De Caterina RD, Ghiadoni L, Taddei S et al. Soluble E-selectin in essential hypertension: A correlate of vascular structural changes. *Am J Hypertens* 2001; 14(3): 259–266.
155. Boos CJ, Lane DA, Karpha M et al. Circulating endothelial cells, arterial stiffness, and cardiovascular risk stratification in hypertension. *Chest* 2007; 132(5): 1540–1547.
156. Eirin A, Zhu XY, Woollard JR et al. Increased circulating inflammatory endothelial cells in blacks with essential hypertension. *Hypertension* 2013; 62(3): 585–591.
157. Nadar SK, Lip GY, Lee KW, Blann AD. Circulating endothelial cells in acute ischaemic stroke. *Thromb Haemostasis* 2005; 94(4): 707–712.
158. Narin N, Yilmaz E, Pamukcu O et al. Are endothelial microparticles early markers of pulmonary hypertension? *Biomarkers* 2014; 19(4): 319–325.
159. Amabile N, Heiss C, Chang V et al. Increased CD62e(+) endothelial microparticle levels predict poor outcome in pulmonary hypertension patients. *J Heart Lung Transplant* 2009; 28(10): 1081–1086.
160. Amabile N, Heiss C, Real WM et al. Circulating endothelial microparticle levels predict hemodynamic severity of pulmonary hypertension. *Am J Respir Crit Care Med* 2008; 177(11): 1268–1275.
161. Hsu CY, Huang PH, Chiang CH et al. Increased circulating endothelial apoptotic microparticle to endothelial progenitor cell ratio is associated with subsequent decline in glomerular filtration rate in hypertensive patients. *PLOS ONE* 2013; 8(7): e68644.
162. Wang JM, Su C, Wang Y et al. Elevated circulating endothelial microparticles and brachial-ankle pulse wave velocity in well-controlled hypertensive patients. *J Hum Hypertens* 2009; 23(5): 307–e68315.
163. Giannotti G, Doerries C, Mocharla PS et al. Impaired endothelial repair capacity of early endothelial progenitor cells in prehypertension: Relation to endothelial dysfunction. *Hypertension* 2010; 55(6): 1389–1397.
164. MacEneaney OJ, DeSouza CA, Weil BR et al. Prehypertension and endothelial progenitor cell function. *J Hum Hypertens* 2011; 25(1): 57–62.
165. Mandraffino G, Sardo MA, Riggio S et al. Circulating progenitor cells are increased in newly diagnosed untreated hypertensive patients with arterial stiffening but normal carotid intima-media thickness. *Hypertens Res* 2011; 34(7): 876–883.
166. Yang Z, Chen L, Su C et al. Impaired endothelial progenitor cell activity is associated with reduced arterial elasticity in patients with essential hypertension. *Clin Exp Hypertens* 2010; 32(7): 444–452.
167. Watson T, Goon PK, Lip GY. Endothelial progenitor cells, endothelial dysfunction, inflammation, and oxidative stress in hypertension. *Antioxid Redox Signal* 2008; 10(6): 1079–1088.
168. Huang PH, Huang SS, Chen YH et al. Increased circulating CD31+/annexin V+ apoptotic microparticles and decreased circulating endothelial progenitor cell levels in hypertensive patients with microalbuminuria. *J Hypertens* 2010; 28(8): 1655–1665.
169. Lee CW, Huang PH, Huang SS et al. Decreased circulating endothelial progenitor cell levels and function in essential hypertensive patients with electrocardiographic left ventricular hypertrophy. *Hypertens Res* 2011; 34(9): 999–1003.

170. Magen E, Feldman A, Cohen Z et al. Circulating endothelial progenitor cells, Th1/Th2/Th17-related cytokines, and endothelial dysfunction in resistant hypertension. *Am J Med Sci* 2010; 339(2): 117–122.
171. Oliveras A, de la Sierra A, Martinez-Estrada OM et al. Putative endothelial progenitor cells are associated with flow-mediated dilation in refractory hypertensives. *Blood Press* 2008; 17(5–6): 298–305.
172. Oliveras A, Soler MJ, Martinez-Estrada OM et al. Endothelial progenitor cells are reduced in refractory hypertension. *J Hum Hypertens* 2008; 22(3): 183–190.
173. de Cavanagh EM, Gonzalez SA, Inserra F et al. Sympathetic predominance is associated with impaired endothelial progenitor cells and tunneling nanotubes in controlled-hypertensive patients. *Am J Physiol Heart Circ Physiol* 2014; 307(2): H207–H215.
174. Juonala M, Viikari JS, Ronnema T et al. Elevated blood pressure in adolescent boys predicts endothelial dysfunction: The cardiovascular risk in young Finns study. *Hypertension* 2006; 48(3): 424–430.
175. Jurva JW, Phillips SA, Syed AQ et al. The effect of exertional hypertension evoked by weight lifting on vascular endothelial function. *J Am Coll Cardiol* 2006; 48(3): 588–589.
176. Shimbo D, Muntner P, Mann D et al. Endothelial dysfunction and the risk of hypertension: The multi-ethnic study of atherosclerosis. *Hypertension* 2010; 55(5): 1210–1216.
177. Sander M, Chavoshan B, Victor RG. A large blood pressure-raising effect of nitric oxide synthase inhibition in humans. *Hypertension* 1999; 33(4): 937–942.
178. Rossi R, Chiurlia E, Nuzzo A et al. Flow-mediated vasodilation and the risk of developing hypertension in healthy postmenopausal women. *J Am Coll Cardiol* 2004; 44(8): 1636–1640.
179. Taddei S, Virdis A, Mattei P et al. Defective L-arginine-nitric oxide pathway in offspring of essential hypertensive patients. *Circulation* 1996; 94(6): 1298–1303.
180. Mordi I, Mordi N, Delles C, Tzemos N. Endothelial dysfunction in human essential hypertension. *J Hypertens* 2016; 34(8): 1464–1472.
181. Bruno RM, Picano E. *Endothelial Function in the Stress Echocardiography Laboratory*. Springer, Cham; 2015.



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*A. Bosch and Roland E. Schmieder*

## INTRODUCTION

Arterial hypertension is characterised by increased total peripheral resistance predominantly caused by changes of small arteries and arterioles (1). These small-resistance arteries are key elements in the vascular control of blood pressure, and structural changes in the microcirculation profoundly influence vascular resistance and thereby blood pressure in the systemic circulation. The retinal circulation is easily accessible by funduscopy and more advanced optical devices, and therefore offers a unique opportunity to visualise the microvasculature in humans *in vivo*. This chapter focusses on hypertensive retinopathy and related retinal arteriolar as well as capillary changes due to hypertension.

## VASCULAR REMODELLING

Vascular remodelling represents an early response mechanism to increased blood pressure and has been identified as a predictor of hypertensive end-organ damage (2). In the early stages, effective antihypertensive treatment has been shown to be capable of reversing vascular remodelling (3).

Vascular remodelling can be distinguished in eutrophic and hypertrophic remodelling. Both types are characterised by an increased media-to-lumen ratio of small arterioles. In eutrophic remodelling, smooth muscle cells are rearranged around a narrowed lumen, which is characterised by a reduced outer vessel and inner lumen diameter but an unchanged media cross-sectional area (4). Conversely, hypertrophic remodelling is caused by an enhanced growth response, resulting in an increased media cross-sectional area. Whereas eutrophic remodelling predominantly occurs in patients with mild to moderate hypertension, patients with severe and longstanding hypertension often develop hypertrophic remodelling (4).

Vascular remodelling of peripheral arterial resistance vessels was first invasively assessed via gluteal biopsies (5). However, more than 40 years ago, Keith et al. identified the retinal vessels as an interesting target to noninvasively observe vessel changes. He wrote 'because the arterioles are small and are difficult to visualise in the peripheral

organs [...], the retina, as seen through the ophthalmoscope, offers a unique opportunity for observing these small vessels [...]' (6). Since that first description, a great deal of additional evidence has been gained supporting the concept that retinal arterioles are important targets to assess altered arteriolar function throughout the human body. Different grading systems stratifying the severity of retinal signs of hypertensive retinopathy have been introduced in internal medicine with the concept that hypertensive retinopathy signs (e.g. arteriolar narrowing or arteriovenous nicking) are independently associated with increased cardiovascular risk (7). However, grade I and II hypertensive retinopathy showed a weak association with other hypertensive organ damage, and the reproducibility of some grading systems remained questionable (e.g. 20–40% interobserver variability) (8). Therefore, new and more specific approaches were introduced in the past decade to detect reliable early changes of the retinal circulation and overcome the previous shortcomings. For instance, in patients with arterial hypertension and short-time diabetes mellitus, eutrophic retinal arteriolar remodelling has been demonstrated using scanning laser Doppler flowmetry (SLDF) (9).

## RETINAL PHOTOGRAPHS/FUNDUSCOPY

It has been shown in several large-scale, population-based longitudinal studies that non-mydratic retinography is able to detect many hypertension-associated retinal microvascular abnormalities. Standardised protocols of retinal photographs (45° nonstereoscopic colour retinal photograph centred between the optic disc and the macula) allow staged classifications on the presence and severity of various retinal vascular abnormalities. The most widely cited classification of hypertensive retinopathy was provided by Keith-Wagener-Barker and is defined by four grades of retinal damage: grade 1 (narrowing), grade 2 (arteriovenous crossings), grade 3 (haemorrhages and exudates) and grade 4 (papilledema) (6,10). However, this classification is not adequately sensitive to differentiate grade 1 from grade 2 in daily clinical practice (11). Therefore, a simplified grading system has been proposed



by Mitchell-Wong combining grades 1 and 2 of the previous classification in one stage (12). A further development, with the aim to increase general reproducibility, used the imaging software Integrative Vessel Analysis (IVAN) (University of Wisconsin, Madison, Wisconsin, USA). This system conducts semi-automated measurement of retinal arterioles and venules and derives its ratio (A/V ratio) as the key parameter of the analysis. Unfortunately, this system is not able to measure the retinal vascular wall directly (7). Based on this work, the Atherosclerosis Risk in Communities (ARIC) Study developed standardised protocols to photograph and grade retinal vascular changes and to analyse their relationship with blood pressure, target-organ damage and cardiovascular events. It has been repeatedly shown that retinal alterations are strongly correlated with past, current and incident hypertension (7). In many large-scale longitudinal studies, associations of directly assessed (generalised) arteriolar narrowing or a decreased A/V ratio (indirectly indicative of proposed arteriolar narrowing) with arterial hypertension were reported. The A/V ratio has also been shown to decline with age, and turned out to be lower in current smokers compared to nonsmokers.

In contrast, conflicting results with respect to the relation of retinal venules with hypertension were found. Whereas some studies showed an association between hypertension and venular narrowing, others demonstrated a correlation between new onset of hypertension and venular widening.

Other retinal digital image analysis focused on the evaluation of bifurcation of retinal vessels and found an increase of tortuosity indices in treatment-naïve hypertensive patients compared to normotensive controls (13).

Regarding the association of A/V ratio and target-organ damage, data are limited. In 1439 middle-aged African American participants of the ARIC study, A/V ratio was associated with left ventricular hypertrophy, which was partly explained by the coexistence of additional cardiovascular risk factors (14). In contrast, in an Italian study comprising 386 untreated and treated hypertensive patients, no difference in A/V ratio between presence and absence of hypertensive organ damage was found (15). Interestingly, the Rotterdam Study identified an

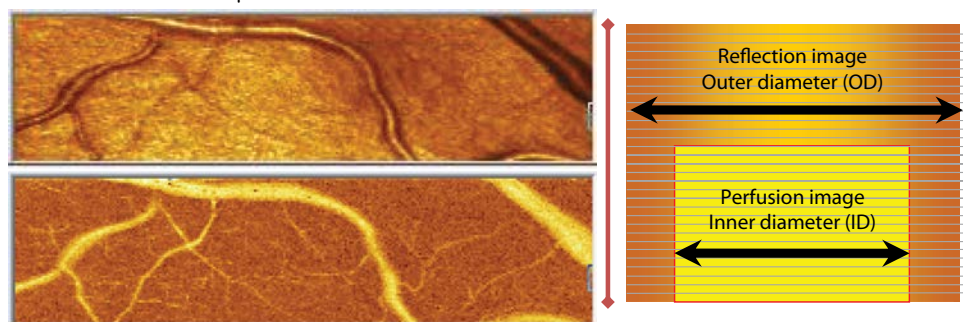
association between venular widening (but not arteriolar narrowing) and incident stroke (16). Nevertheless, the assessment of A/V ratio is widely accepted as a measure of hypertensive retinopathy in clinical research.

## SCANNING LASER DOPPLER FLOWMETRY

Beyond the inability to separately quantify arteriolar and venular alterations, funduscopic photographs are also not able to visualise the inner and outer wall of retinal vessels (7). One promising approach was introduced to the field of hypertension by our study group in 2001. SLDF assesses functional (i.e. perfusion) and structural (i.e. rearrangement of vascular smooth muscle cells) parameters of the retinal circulation at the same time (17). In brief, SLDF is performed in the juxtapupillary area of the right eye, 2–3 mm temporal superior to the optic nerve at 670 nm (Heidelberg Retina Flowmeter, Heidelberg Engineering, Germany). An arteriole (80–140  $\mu\text{m}$ ) of the superficial retinal layer in a retinal sample of  $2.56 \times 0.64 \times 0.30 \text{ mm}$  is scanned within 2 seconds (one systolic and one diastolic phase) and measured every 10  $\mu\text{m}$  of this specific length of the arteriole (Figure 34.1). The confocal technique of the device ensures that only capillary flow of the superficial layer of 300  $\mu\text{m}$  is measured.

This approach allows the *in vivo* measurement of the outer arteriolar diameter (OD) in reflection images and the inner lumen diameter (ID) in perfusion images and thus the assessment of early vascular remodelling of retinal arterioles by calculating wall-to-lumen ratio (WLR) using the formula  $(\text{OD} - \text{ID})/\text{ID}$  (18,19). There is evidence that WLR of retinal arterioles is closely related to the micromyographic measurements of the media-to-lumen ratio of subcutaneous small arteries taken from bottom biopsies, which are known to predict cardiovascular events (20,21). There are further investigations pointing towards evidence that retinal arterioles undergo similar changes as peripheral and cerebral arterioles in hypertension, indicating that retinal abnormalities mirror structural and functional microvascular changes in hypertensive

Retinal arterioles: 80–140  $\mu\text{m}$



$$\text{Wall-thickness (WT)} = \text{OD} - \text{ID}/2$$

$$\text{Cross-sectional area (CA)} = 3.14 \times (\text{OD}^2 - \text{ID}^2)/4$$

$$\text{Wall-to-lumen ratio (WLR)} = (\text{OD} - \text{ID})/\text{ID}$$

**Figure 34.1** Scanning laser Doppler flowmetry (SLDF) of retinal arterioles: Scanned area with reflection and perfusion image, calculation of the wall-to-lumen ratio, cross-sectional area and wall thickness.

end-organs (9,22,23). It is noteworthy that SLDF does not require mydriatic drug application for pupil dilatation. On the contrary, local application of tropicamide is known to affect retinal perfusion and vascular tone and should therefore not be applied when using SLDF (24). Reliability of SLDF measurements have been repeatedly shown to be acceptable and similar to other biomarkers (coefficient of variation <10%) (18,25).

## RETINAL CAPILLARY FLOW

For perfusion analysis, retinal capillary vessels with diameter  $\leq 20 \mu\text{m}$  are selected. Retinal capillary flow (RCF) is assessed using SLDF (Figure 34.2), and blood flow is calculated independently by the automatic full field perfusion image analyser (AFFPIA) (26). Further dynamic information (e.g. basal nitric oxide [NO] activity) of the retinal capillaries can be assessed by measuring changes of RCF before and after administration of the NO synthase inhibitor  $\text{N}^G$ -monomethyl-L-arginine (L-NMMA). Furthermore, to assess vasodilatory capacity of the retinal vessels, flicker light can be applied, which is known to cause vasodilation without affecting systemic blood pressure.

It has been shown that systolic blood pressure is inversely related to the percent increase of RCF due to flicker-light exposure, independently of other cardiovascular risk factors (27). In young hypertensive patients, basal NO activity assessment revealed an impaired endothelial function in the retinal circulation, which was improved after treatment with an angiotensin-receptor blocker (17). However, short-time antihypertensive treatment was not able to improve basal NO activity in the retinal circulation in elderly hypertensive patients (28). We were previously able to demonstrate that vasodilatory capacity (RCF change due to flicker-light) was lower in (untreated) hypertensive patients compared to normotensive controls.

In a further development step, the pulsatile pattern of RCF of retinal arterioles in systole and diastole could be reliably assessed. Pulsed RCF is defined as the difference in RCF between systole and diastole. In a first study, patients with treatment-resistant hypertension exhibited an exaggerated pulsed RCF compared to patients

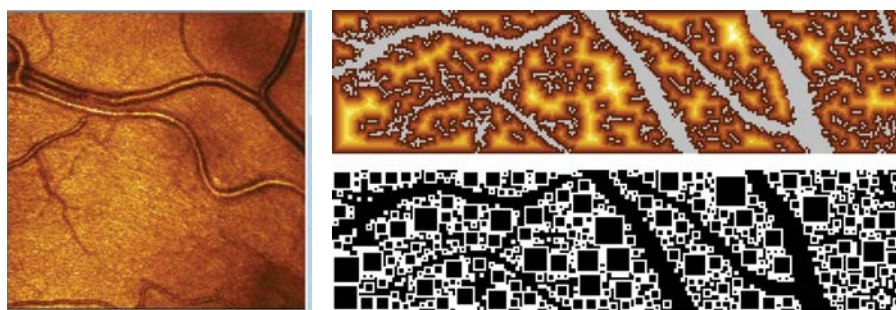
with hypertension stage 1–2 (29). Six months after renal denervation, a decrease of pulsed RCF was observed in parallel to a decrease of blood pressure and heart rate, suggesting a reduction of shear stress on the vascular wall (30). The importance of these findings is emphasized by the most recent data that excessive flow pulsatility damages the cerebral microcirculation, leading to impaired cognitive function (31).

## CAPILLARY RAREFACTION

The analysis of retinal arterioles has lately been extended to assess parameters of retinal capillary rarefaction by the SLDF technique and based on RCF measurements (Figure 34.2). Since the assessment of retinal capillary rarefaction is flow-dependent, a distinction between functional and structural capillary rarefaction is not possible. The measurement includes the assessment of intercapillary distance (defined as distance between two pixels localised in a capillary) and capillary area (32) (Figure 34.2). The first result was, in accordance with the literature reporting of capillary rarefaction in other vascular beds, that patients with arterial hypertension stage 1 or 2 showed capillary rarefaction compared to healthy individuals. In addition, it has been shown that short-term treatment with valsartan in hypertension stage 1 or 2 improves retinal capillary rarefaction to a level that is statistically not different from healthy individuals (33).

## WALL-TO-LUMEN RATIO: PREDICTIVE VALUE OF END-ORGAN DAMAGE

Several studies have confirmed the prognostic significance of retinal vascular abnormalities for mortality attributed to a cardiovascular cause (9,12,34). Vascular remodelling, characterised by an increased WLR of small resistance and large arteries, has been identified as one of the early processes that occurs in response to increased blood pressure, and reflects early hypertensive end-organ damage (2,20,35,36). Hypertensive patients with a history of



Capillary pixel: Vessel  $< 20 \mu\text{m}$

Inter-capillary distance: Distance of one pixel in a capillary to the next pixel in a capillary

Capillary area: Area of vessels  $< 20 \mu\text{m}$

**Figure 34.2** Scanning laser Doppler flowmetry (SLDF) for calculation of capillary rarefaction: Definition and calculation of intercapillary distance and capillary area.

cerebrovascular events had an increased WLR of retinal arterioles compared to both treated hypertensive patients and normotensive individuals. Moreover, treated hypertensive patients with poor blood pressure control showed higher WLR than treated hypertensive patients with good blood pressure control (37). In addition, never-treated hypertensive patients revealed higher WLR than normotensive individuals (23). A current consensus article from the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) mentions retinal WLR as a parameter for the noninvasive evaluation of the microvasculature and states that future studies will have to assess the prognostic contribution of noninvasively assessing the microvascular bed in patients with hypertension (38).

### ADAPTIVE OPTICS IMAGING

Adaptive optics imaging has been shown to be a reliable method to noninvasively assess retinal microvascular changes. The adaptive optics retinal fundus camera creates a retinal image over time by recording scattered light from a focused beam, and produces  $4^\circ \times 4^\circ$  high-resolution fundus images (39). By continuous scanning of the retina in a raster, it is possible to take images of large areas at a faster rate (40 fundus images in 4 seconds) than with conventional flash fundus imaging (40,41). Adaptive optics imaging can be used to describe qualitative (e.g. hard exudates, microaneurysms) and quantitative (e.g. capillary diameter, WLR) adaptive changes to increased blood pressure (42) (Figure 34.3). The feasibility and reproducibility of retinal arteriole imaging was demonstrated in healthy individuals with several cardiovascular risk factors (43) and in untreated hypertensive patients (44). It has also been shown that adaptive optics–based assessment of WLR was positively correlated with age, mean blood pressure and body mass index (43). The quantitative measurements of WLR measurements by adaptive optics imaging are close to those reported by SLDF (21,23,41). Analysis of WLR using adaptive optics imaging in 1500 subjects showed that a WLR higher than 0.31 is indicative of hypertension and a lumen diameter of less than  $78 \mu\text{m}$  of masked hypertension (45). Adaptive optics imaging showed that baroreceptor activation therapy reduced wall-cross-sectional area

by 12% (46). Nevertheless, no validation of the method in respect to other available techniques (e.g. media-to-lumen ratio of subcutaneous arterioles) is yet provided (7). Of note, with adaptive optics imaging, RCF cannot be measured and thus dynamic measurements of flow in response to pharmacologic or physiologic stimulus cannot be assessed.

### OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) has been developed for noninvasive cross-sectional imaging in an enhanced resolution within an acceptable time period. OCT uses low-coherence interferometry to produce a two-dimensional image of optical scattering from internal tissue microstructures in a way that is analogous to ultrasonic pulse-echo imaging (47). In addition to its diagnostic use in various ophthalmologic diseases, OCT has emerged as tool to assess structural compounds involved in neurodegeneration that contribute to neurologic disability in a variety of central nervous system diseases (48). Currently, as a clinical tool, OCT is particularly useful for the structural measurement of peripapillary retinal nerve fibre layer thickness, optic nerve head volumetric analysis and macular anatomy (49). Schuster et al. proposed OCT-based retinal vessel analysis for the evaluation of hypertensive vasculopathy (50). They demonstrated a relationship between blood pressure and OCT-based arterial-venous ratio (11). However, data about the retinal vessel parameters in arterial hypertension are limited. In an analysis of patients aged over 50 years, it was shown that mean arteriolar outer and inner diameter did not differ between patients with ( $n = 103$ ) and without hypertension ( $n = 83$ ) but mean arterial wall thickness was significantly larger (51). This is in line with previous findings using SLDF in never-treated hypertensive patients compared to controls (23). In addition, in patients with poor blood pressure control ( $\text{BP} \geq 140/90 \text{ mmHg}$ ), calculation of OCT-measured WLR ( $0.396 \pm 0.16$ ) was similar to those measured using SLDF (37,51), but no direct comparison has thus far been made. In addition, retinal microvascular damage assessed with OCT in patients with obstructive sleep apnoea (OSAS) and hypertension was associated with OSAS severity (52).

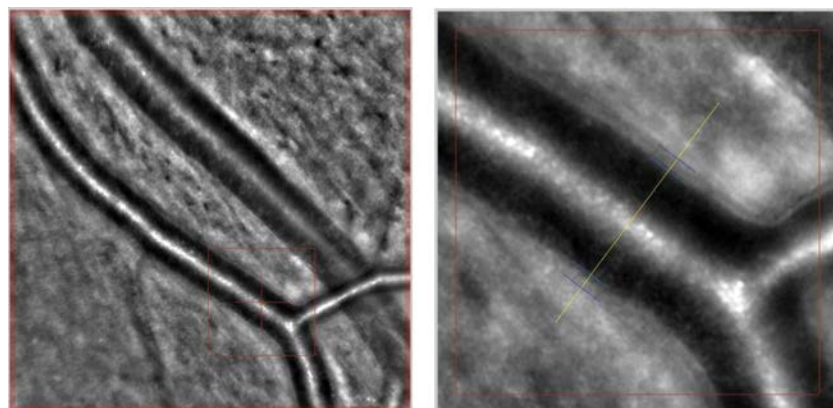


**Figure 34.3** Adaptive optics imaging: Analysis of retinal arterioles with measurement of inner and outer vessel diameter.



## REFERENCES

- Lehmann MV, Schmieder RE. Remodeling of retinal small arteries in hypertension. *Am J Hypertens* 2011; 24(12): 1267–1273.
- Mulvany MJ. Small artery remodelling in hypertension: Causes, consequences and therapeutic implications. *Med Biol Eng Comput* 2008; 46(5): 461–467.
- Feihl F, Liaudet L, Levy BI, Waeber B. Hypertension and microvascular remodelling. *Cardiovasc Res* 2008; 78(2): 274–285.
- Rizzoni D, Rosei EA. Small artery remodeling in diabetes mellitus. *Nutr Metab Cardiovasc Dis* 2009; 19(8): 587–592.
- Park JB, Schiffrin EL. Small artery remodeling is the most prevalent (earliest?) form of target organ damage in mild essential hypertension. *J Hypertens* 2001; 19(5): 921–930.
- Keith NM, Wagener HP, Barker NW. Some different types of essential hypertension: Their course and prognosis. *Am J Med Sci* 1974; 268(6): 336–345.
- Ott C. Retinal circulation in arterial disease. In: Berbari A, Mancia G (eds). *Arterial Disorders*. Springer; 2015.
- Dimmitt SB, West JN, Eames SM et al. Usefulness of ophthalmoscopy in mild to moderate hypertension. *Lancet* 1989; 1(8647): 1103–1106.
- Jumar A, Ott C, Kistner I et al. Early signs of end-organ damage in retinal arterioles in patients with type 2 diabetes compared to hypertensive patients. *Microcirculation* 2016; 23(6): 447–455.
- Cuspidi C, Sala C, Grassi G. Updated classification of hypertensive retinopathy: Which role for cardiovascular risk stratification? *J Hypertens* 2015; 33(11): 2204–2206.
- Konstantinidis L, Guex-Crosier Y. Hypertension and the eye. *Curr Opin Ophthalmol* 2016; 27(6): 514–521.
- Wong TY, Mitchell P. Hypertensive retinopathy. *N Engl J Med* 2004; 351(22): 2310–2317.
- Triantafyllou A, Al-Diri B, Anyfanti P et al. 7d.08: Detecting hypertensive retinopathy using retinal vascular geometry. *J Hypertens* 2015; (33 Suppl 1): e102.
- Tikellis G, Arnett DK, Skelton TN et al. Retinal arteriolar narrowing and left ventricular hypertrophy in African Americans. The Atherosclerosis Risk in Communities (ARIC) Study. *Am J Hypertens* 2008; 21(3): 352–e109.
- Masaidi M, Cuspidi C, Giudici V et al. Is retinal arteriolar-venular ratio associated with cardiac and extracardiac organ damage in essential hypertension? *J Hypertens* 2009; 27(6): 1277–1283.
- Ikram MK et al. Retinal vessel diameters and risk of stroke: The Rotterdam Study. *Neurology* 2006; 66(9): 1339–1343.
- Delles C, Michelson G, Harazny J et al. Impaired endothelial function of the retinal vasculature in hypertensive patients. *Stroke* 2004; 35(6): 1289–1293.
- Harazny JM, Raff U, Welzenbach J et al. New software analyses increase the reliability of measurements of retinal arterioles morphology by scanning laser Doppler flowmetry in humans. *J Hypertens* 2011; 29(4): 777–782.
- Ritt M, Schmieder RE. Wall-to-lumen ratio of retinal arterioles as a tool to assess vascular changes. *Hypertension* 2009; 54(2): 384–387.
- Ott C, Schmieder RE. Blood pressure and retinal small arteries. *J Hypertens* 2013; 31(10): 1946–1947.
- Rizzoni D, Porteri E, Duse S et al. Relationship between media-to-lumen ratio of subcutaneous small arteries and wall-to-lumen ratio of retinal arterioles evaluated noninvasively by scanning laser Doppler flowmetry. *J Hypertens* 2012; 30(6): 1169–1175.
- Heagerty AM, Aalkjaer C, Bund SJ et al. Small artery structure in hypertension. Dual processes of remodeling and growth. *Hypertension* 1993; 21(4): 391–397.
- Ritt M, Harazny JM, Ott C et al. Analysis of retinal arteriolar structure in never-treated patients with essential hypertension. *J Hypertens* 2008; 26(7): 1427–1434.
- Harazny JM, Schmieder RE, Welzenbach J, Michelson G. Local application of tropicamide 0.5% reduces retinal capillary blood flow. *Blood Press* 2013; 22(6): 371–376.
- Kreis AJ, Nguyen T, Rogers S et al. Reliability of different image analysis methods for scanning laser Doppler flowmetry. *Curr Eye Res* 2008; 33(5): 493–499.
- Michelton G, Welzenbach J, Pal I, Harazny J. Automatic full field analysis of perfusion images gained by scanning laser Doppler flowmetry. *Br J Ophthalmol* 1998; 82(11): 1294–1300.
- Ritt M, Harazny JM, Ott C et al. Impaired increase of retinal capillary blood flow to flicker light exposure in arterial hypertension. *Hypertension* 2012; 60(3): 871–876.
- Oehmer S, Harazny J, Delles C et al. Valsartan and retinal endothelial function in elderly hypertensive patients. *Blood Press* 2006; 15(3): 185–191.
- Harazny JM, Ott C, Raff U et al. First experience in analysing pulsatile retinal capillary flow and arteriolar structural parameters measured noninvasively in hypertensive patients. *J Hypertens* 2014; 32(11): 2246–2252, discussion 52.
- Ott C, Harazny JM, Schmid A et al. Retinal microperfusion after renal denervation in treatment-resistant hypertensive patients. *Clin Res Cardiol* 2015; 104(9): 782–789.
- Wohlfahrt P et al. Large artery stiffness and carotid flow pulsatility in stroke survivors. *J Hypertens* 2014; 32(5): 1097–1103, discussion 103.
- Jumar A, Harazny JM, Ott C et al. Retinal capillary rarefaction in patients with type 2 diabetes mellitus. *PLOS ONE* 2016; 11(12): e0162608.
- Jumar A, Harazny JM, Ott C et al. Improvement in retinal capillary rarefaction after valsartan treatment in hypertensive patients. *J Clin Hypertens* 2016; 18(11): 1112–1118.
- Witt N, Wong TY, Hughes AD et al. Abnormalities of retinal microvascular structure and risk of mortality from ischemic heart disease and stroke. *Hypertension* 2006; 47(5): 975–981.
- Izzard AS, Rizzoni D, Agabiti-Rosei E, Heagerty AM. Small artery structure and hypertension: Adaptive changes and target organ damage. *J Hypertens* 2005; 23(2): 247–250.
- Mulvany MJ, Baumbach GL, Aalkjaer C et al. Vascular remodeling. *Hypertension* 1996; 28(3): 505–506.
- Harazny JM et al. Increased wall:lumen ratio of retinal arterioles in male patients with a history of a cerebrovascular event. *Hypertension* 2007; 50(4): 623–629.
- Perrone-Filardi P, Coca A, Galderisi M et al. Noninvasive cardiovascular imaging for evaluating subclinical target organ damage in hypertensive patients: A consensus article from the European Association of Cardiovascular Imaging, the European Society of Cardiology Council on Hypertension and the European Society of Hypertension. *J Hypertens* 2017; 35(9): 1727–1741.
- Sahin B, Lamory B, Levecq X et al. Adaptive optics with pupil tracking for high resolution retinal imaging. *Biomed Opt Express* 2012; 3(2): 225–239.
- Roorda A, Romero-Borja F, Donnelly Iii W et al. Adaptive optics scanning laser ophthalmoscopy. *Opt Express* 2002; 10(9): 405–412.
- Koch E, Rosenbaum D, Brolly A et al. Morphometric analysis of small arteries in the human retina using adaptive optics imaging: Relationship with blood pressure and focal vascular changes. *J Hypertens* 2014; 32(4): 890–898.
- Burns SA, Elsner AE, Chui TY et al. In vivo adaptive optics microvascular imaging in diabetic patients without clinically severe diabetic retinopathy. *Biomed Opt Express* 2014; 5(3): 961–974.
- Meixner E, Michelson G. Measurement of retinal wall-to-lumen ratio by adaptive optics retinal camera: A clinical research. *Graefes Arch Clin Exp Ophthalmol* 2015; 253(11): 1985–1995.
- Rosenbaum D, Koch E, Girerd X et al. [Imaging of retinal arteries with adaptive optics, feasibility and reproducibility]. *Ann Cardiol Angeiol* 2013; 62(3): 184–188.
- Gallo A, Mattina A, Rosenbaum D et al. Retinal arteriolar remodeling evaluated with adaptive optics camera: Relationship with blood pressure levels. *Ann Cardiol Angeiol* 2016; 65(3): 203–207.
- Gallo A, Rosenbaum D, Kanagasabapathy C, Girerd X. Effects of carotid baroreceptor stimulation on retinal arteriole remodeling evaluated with adaptive optics camera in resistant hypertensive patients. *Ann Cardiol Angeiol* 2017; 66(3): 165–170.
- Huang D, Swanson EA, Lin CP et al. Optical coherence tomography. *Science* 1991; 254(5035): 1178–1181.
- Costello F. Optical Coherence Tomography in neuro-ophthalmology. *Neurol Clin* 2017; 35(1): 153–163.
- Nolan RC, Narayana K, Galetta SL, Balcer LJ. Optical coherence tomography for the neurologist. *Semin Neurol* 2015; 35(5): 564–577.
- Schuster AK, Fischer JE, Vossmerbaeumer C, Vossmerbaeumer U. Optical coherence tomography-based retinal vessel analysis for the evaluation of hypertensive vasculopathy. *Acta Ophthalmol* 2015; 93(2): e148–e153.
- Muraoka Y, Tsujikawa A, Kumagai K et al. Age- and hypertension-dependent changes in retinal vessel diameter and wall thickness: An optical coherence tomography study. *Am J Ophthalmol* 2013; 156(4): 706–714.
- Wang XY, Li M, Ding X, Han DM. [Application of optical coherence tomography angiography in evaluation of retinal microvascular changes in patients with obstructive sleep apnea syndrome]. *Zhonghua Yi Xue Za Zhi* 2017; 97(32): 2501–2505.



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# Section VI

## Integrated Diagnostic Aspects

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# THE INTEGRATED DIAGNOSTIC APPROACH IN GENERAL MEDICINE

# 35

*Andrzej Wićcek, Aleksander Prejbisz and Andrzej Januszewicz*

## INTRODUCTION

It is recommended to obtain comprehensive medical history and physical examination in all patients with hypertension, aiming at:

- Confirmation the diagnosis of hypertension
- Detection of secondary forms of hypertension
- Assessment of cardiovascular (CV) risk, hypertension-mediated organ damage (HMOD) and concomitant clinical conditions

In most patients this goal can be achieved through blood pressure (BP) measurement, assessment of medical history including family history, physical examination, and both routine as well as additional diagnostic tests ([Table 35.1](#)). As shown in [Table 35.2](#), based on ESC/ESH 2018 guidelines, most factors influencing prognosis used for stratification of total CV risk can be evaluated by patient's medical history, physical examination, BP measurement and routine diagnostic tests, which are widely available and easy to complete ([1](#)).

Despite the importance of the HMOD as a marker of higher CV risk, availability of appropriate techniques is limited. The ESC/ESH 2018 recommended that basic screening for HMOD should be performed in all hypertensive patients and more detailed assessment should be performed when the presence of HMOD would influence treatment decisions. 2016 European Guidelines on cardiovascular disease prevention advocated, in particular, assessment of albuminuria and echocardiography, which may improve risk prediction, especially in patients at moderate risk ([1,2](#)).

In this chapter, selected topics related to the assessment of medical history, physical examination, BP level evaluation and routine diagnostic tests in relation to confirmation of the diagnosis of hypertension, detection of secondary forms of hypertension and assessment of CV risk are discussed.

## MEDICAL HISTORY

The assessment of medical history in hypertensive subjects should include:

- Duration of hypertension, previous and highest levels of BP, including measurements at home
- Previous and current antihypertensive management
- Symptoms of secondary forms of hypertension ([Table 35.3](#))
- Evaluation of risk factors
- History and symptoms of OD and CV disease

The first diagnosis of hypertension, course of BP, current and past BP levels and current and past antihypertensive medications should be addressed. In particular, attention should be paid to evidence of adherence or lack of adherence to the therapy. Efficacy and adverse effects of antihypertensive drugs should be assessed ([1](#)).

Various symptoms related to identifiable causes of hypertension can be obtained from a medical history assessment ([Table 35.3](#)). Intake of drugs/substances which may affect BP levels and/or hypertension control, e.g. liquorice, gluco- and mineralocorticosteroids, nonsteroidal anti-inflammatory drugs, vasoconstrictive nasal drops, carbenoxolone, cocaine, yohimbine amphetamines, erythropoietin and cyclosporine, should also be discussed with the patient ([1](#)).

In women, use of oral contraceptives and hormonal replacement therapy should be evaluated including type, dose, formulation, duration of use and relationship with increases in BP. Women should also be asked about history of pre-eclampsia and/or pregnancy-induced hypertension, since those conditions are related to increased risk of hypertension development and CV risk ([2](#)).

A detailed history of CV risk factors and diseases should be obtained from all patients, to allow assessment of CV risk. For evaluation of CV risk factors, medical history evaluation should include:

**Table 35.1** Routine tests and additional tests, based on history, physical examination and findings from routine laboratory tests in hypertensive patients

| Routine tests                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Additional tests                                                                                                                                                                                                                                                                                         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>■ Haemoglobin and/or haematocrit</li> <li>■ Fasting plasma glucose and glycated HbA1C</li> <li>■ Serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol</li> <li>■ Serum triglycerides</li> <li>■ Serum potassium and sodium</li> <li>■ Serum uric acid</li> <li>■ Serum creatinine (with estimation of GFR)</li> <li>■ Blood liver function tests</li> <li>■ Urine analysis: microscopic examination; urinary protein by dipstick test; or, ideally, albumin:creatinine ratio</li> <li>■ 12-lead ECG</li> </ul> | <ul style="list-style-type: none"> <li>■ Fundoscopy</li> <li>■ Echocardiogram</li> <li>■ Carotid ultrasound</li> <li>■ Abdominal ultrasound and Doppler studies</li> <li>■ Pulse wave velocity</li> <li>■ Ankle-brachial index</li> <li>■ Cognitive function testing</li> <li>■ Brain imaging</li> </ul> |

Source: Based on ESC/ESH 2018 Guidelines.

- Recent weight changes, obesity
- History of diabetes mellitus (family and personal history, medications, blood glucose levels)
- History of dyslipidaemia (family and personal history, medications, blood lipid levels)
- Dietary habits (including sodium and potassium intake)
- Amount of physical exercise
- Smoking habits
- Alcohol intake

A history of cerebrovascular disease should include headache, vertigo, impaired vision, sensory or motor deficits, cognitive dysfunction, carotid revascularization and neurological disorders with an emphasis on transient ischaemic attack and stroke.

A comprehensive history of cardiac disease should be evaluated, including symptoms such as chest pain, shortness of breath, swollen ankles, syncope and palpitations as well as history of coronary revascularization, myocardial infarction, valvular heart disease, heart failure and arrhythmias (especially atrial fibrillation).

Peripheral arterial disease can be indicated by specific symptoms, e.g. cold extremities and intermittent claudication. Pain-free walking distance and history of peripheral revascularization should also be evaluated.

A history of chronic kidney disease (CKD) should include symptoms; e.g. polyuria, thirst, nocturia and haematuria as well as the type and duration of kidney disease (acute or chronic).

A family history of early-onset hypertension and/or premature CV disease should be obtained, since it is an important indicator of familial predisposition to hypertension and CV disease. Few rare, monogenic forms of hypertension have been described, such as glucocorticoid-remediable aldosteronism, Liddle syndrome and others. Although essential hypertension is a highly heterogeneous disorder with a multifactorial aetiology, the heritability of

hypertension has been estimated to vary between 35–50% in the majority of studies (1,3–5).

Evaluation of the hypertensive subject should be also directed toward the patient's psychosocial status, including the willingness to make necessary lifestyle changes and to adhere to medical therapy. It is also necessary to assess whether sexual dysfunction is present. Erectile dysfunction might be related to treatment with some antihypertensive drugs, but most likely it is related to the underlying cardiovascular disease. Last but not least, symptoms of depression and anxiety disorders should be also sought after (1,6).

## PHYSICAL EXAMINATION

The goals of physical examinations are establishing or verifying the diagnosis of hypertension, establishing current BP levels (BP measurement – see following section), screening for secondary causes of hypertension and evaluating the presence of CV risk factors (Table 35.4). Height, weight and waist circumference should be measured in the standing position, followed by calculation of body mass index (BMI). All subjects should undergo auscultation of the carotid arteries, heart and renal arteries. Depending on the location, murmurs should advocate further investigations (carotid ultrasound, echocardiography, renal vascular ultrasound) (1).

As increased heart rate is related to an increased risk of heart disease, in all patients, heart rate should be measured (by pulse palpation, at least 30s after the BP second measurement in the sitting position). Pulse palpation and cardiac auscultation may also disclose arrhythmias. An irregular pulse raises the suspicion of atrial fibrillation, including asymptomatic atrial fibrillation (7,8).

## BP MEASUREMENTS

Office BP measurement is recommended for screening and diagnosis of hypertension. It was also recommended that the diagnosis of hypertension should be based on at least three BP measurements per visit and on at least two visits or on out-of-office BP measurements. On at least one occasion, BP should be measured at both arms, and differences between the two arms in systolic BP >20 mmHg and/or in diastolic BP >10 mmHg – if confirmed – should prompt further investigation of vascular abnormalities. Moreover, it has been shown that consistent >15 mmHg systolic BP difference between arms carries an increased CV risk (1,9,10).

It is recommended that BP should be measured 1 and 3 min after assumption of the standing position, especially in elderly patients and subjects with diabetes or other conditions in which orthostatic hypotension may be frequent or suspected. It has been proven that orthostatic hypotension, defined as a reduction in systolic BP of  $\geq 20$  mmHg or in diastolic blood pressure of  $\geq 10$  mmHg within 3 min of standing, carries a worse prognosis for mortality and CV events (11,12).

Based on the BP measurements, pulse pressure (PP) can be calculated by subtracting diastolic BP from systolic BP. There is abundant evidence that the increased PP in elderly subjects is a marker for central artery stiffness. ESC/ESH 2018 defined elevated PP  $\geq 60$  mmHg in the elderly as asymptomatic

**Table 35.2** Factors other than office BP levels influencing prognosis used for stratification of total cardiovascular risk

| Risk factors                                                                                                                                                                                                                                                | Asymptomatic organ damage                                                                                                                                                                                                                                        | Established CV or renal disease                                                                                              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|
| Gender (men > women)                                                                                                                                                                                                                                        | Arterial stiffening: Pulse pressure (in the elderly) $\geq 60$ mmHg                                                                                                                                                                                              | Cerebrovascular disease: Ischaemic stroke; cerebral haemorrhage; transient ischaemic attack                                  |
| Age                                                                                                                                                                                                                                                         | Electrocardiographic LVH (Sokolow – Lyon index $>3.5$ mV; RaVL $>1.1$ mV; Cornell voltage duration product $>244$ mV*ms)                                                                                                                                         | CHD: Myocardial infarction; angina; myocardial revascularization with PCI or CABG                                            |
| Smoking<br>Family history of premature CVD (men aged $<55$ years; women aged $<65$ years)<br>Diabetes<br>Familial or parental history of early-onset hypertension<br>Early onset menopause<br>Sedentary lifestyle<br>Psychosocial and socioeconomic factors | Echocardiographic LVH [LV mass index: men $>50$ g/m <sup>2.7</sup> ; women $>47$ g/m <sup>2.7</sup> (height in m <sup>2.7</sup> ); indexation for BSA may be used in normal-weight patients; LV mass/BSA g/m <sup>2</sup> $>115$ (men) and $>95$ (women)]        | Heart failure, including heart failure with preserved EF                                                                     |
| Total cholesterol and HDL-C<br>Uric acid                                                                                                                                                                                                                    | Advanced retinopathy: haemorrhages or exudates, papilloedema                                                                                                                                                                                                     | Symptomatic lower extremities peripheral artery disease<br>Atrial fibrillation<br>Presence of atheromatous plaque on imaging |
|                                                                                                                                                                                                                                                             | Arterial stiffening: Carotid – femoral PWV $>10$ m/s                                                                                                                                                                                                             |                                                                                                                              |
|                                                                                                                                                                                                                                                             | Ankle-brachial index $<0.9$                                                                                                                                                                                                                                      |                                                                                                                              |
| Overweight or obesity                                                                                                                                                                                                                                       | Microalbuminuria (30–300 mg/24 h) or Albumin – creatinine ratio (30–300 mg/g; 3.4–34 mg/mmol) (preferentially on morning spot urine)<br>Moderate CKD with eGFR $>30$ – $59$ mL/min/1.73 m <sup>2</sup> (BSA) or severe CKD eGFR $<30$ mL/min/1.73 m <sup>2</sup> |                                                                                                                              |
| Heart rate (resting $>80$ beats/min)                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                  |                                                                                                                              |

Note: Factors were highlighted if the particular risk factor is evaluated by patient's medical history (yellow), physical examination (orange), blood pressure measurement (green), routine tests (blue) and additional tests (brown). Based on ESH/ESC 2013 and ESC/ESH 2018 Guidelines.

HMOD. It has been also established that PP is an independent risk factor for CV disease and may improve risk prediction (1,13–15).

Out-of-office BP measurement is assessed by ambulatory BP measurement (ABPM) or home BP measurement (HBPM). BP levels on ABPM and HBPM are more closely related to HMOD than office BP, and CV morbidity and mortality is significantly better predicted by those methods compared to office BP (16,17).

Out-of-office BP measurement (ABPM and/or HBPM) is recommended for a number of clinical indications, including suspicion of white-coat or masked hypertension, quantifying the effects of treatment, and identifying possible causes of side effects (i.e. hypotension) (1).

Advantages and application of ABPM, HBPM and automated office BP measurements are discussed in Chapters 21, 24, and 25.

## GLUCOSE LEVEL EVALUATION

Estimation of fasting plasma glucose (FPG) concentration is recommended in each patient with newly diagnosed arterial hypertension. In hypertensive patients with normal FPG concentration, these measurements should be repeated once every 3 years, but in patients with abnormal FPG concentration once a year. It is also recommended to estimate FPG concentration once a year in hypertensive patients who are overweight/obese, have members of the family with diabetes mellitus, or are older than 45 years. Higher risk for development of diabetes mellitus is also observed in women with polycystic ovary syndrome and in those who delivered a child with body weight greater than 4.0 kg. Oral glucose tolerance test is recommended in patients with FPG above 5.6 mmol/L (100 mg/dL).



**Table 35.3** Abnormalities on basal workup leading to the suspicion of secondary hypertension

| Secondary form of hypertension          | Abnormalities on basal workup                                                                                                                                                                                                                   |                                                                                                  |                                                                                                    |                                                                        |
|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
|                                         | Medical history                                                                                                                                                                                                                                 | Physical examination                                                                             | Routine tests                                                                                      | Screening tests                                                        |
| Obstructive sleep apnea                 | Specific daytime and nighttime symptoms (e.g. snoring, fitful sleep, breathing pauses during sleep, daytime sleepiness)                                                                                                                         | Abdominal obesity<br>Increased neck circumference<br>Craniofacial abnormalities                  | Increased plasma glucose<br>Lipid abnormalities                                                    | Sleep study                                                            |
| Renal parenchymal disease               | History of urinary tract infection or obstruction, haematuria, analgesic abuse; family history of kidney disease                                                                                                                                | Abdominal masses (in cases of polycystic kidney disease), skin pallor                            | Presence of protein, erythrocytes, or leucocytes in the urine<br>Decreased GFR                     | Renal ultrasound                                                       |
| Renal artery stenosis – atherosclerotic | HT of abrupt onset, worsening or increasingly difficult to treat HT<br>Resistant or malignant HT<br>Flash pulmonary oedema                                                                                                                      | Abdominal bruit, bruits over other arteries                                                      | Rapid deterioration in renal function (spontaneous or in response to RAA blockers)<br>Hypokalaemia | Renal duplex Doppler ultrasonography                                   |
| Renal artery stenosis – FMD             | Early-onset HT (especially in women)<br>Worsening or increasingly difficult to treat HT<br>Resistant or malignant HT<br>FMD in other vascular beds or history of spontaneous artery dissection                                                  | Abdominal bruit, bruits over other arteries                                                      | Rapid deterioration in renal function (spontaneous or in response to RAA blockers)<br>Hypokalaemia | Renal duplex Doppler ultrasonography                                   |
| Primary aldosteronism                   | Muscle cramps or weakness<br>Resistant HT<br>HT and:<br>■ Incidental adrenal mass<br>■ OSA<br>■ Family history of early-onset HT and cerebrovascular events at age <40 years<br>■ First-degree relatives of patients with primary aldosteronism | Arrhythmias (especially atrial fibrillation)                                                     | Hypokalaemia (spontaneous or diuretic-induced)                                                     | Aldosterone–renin ratio                                                |
| PPGL                                    | Paroxysmal:<br>■ HT or a crisis superimposed to sustained HT<br>■ Headache, sweating, palpitations and pallor<br>Previous PPGL<br>Family history of PPGL<br>Incidental discovery of adrenal (or in some cases, extra-adrenal) masses            | Skin stigmata of neurofibromatosis (café-au-lait spots, neurofibromas), orthostatic hypotension  | Hyperglycaemia                                                                                     | Plasma-free or 24-h urinary fractionated metanephrines                 |
| Cushing syndrome                        | Rapid weight gain, polyuria, polydipsia, muscle weakness, psychological disturbances                                                                                                                                                            | Typical body habitus (central obesity, moon-face, buffalo hump), red striae, hirsutism, bruising | Hyperglycaemia                                                                                     | 24-h urinary free cortisol<br>Excretion<br>Low-dose dexamethasone test |

Source: Mancia G et al. *J Hypertens* 2013; 31: 1281–1357; Piepoli MF et al. *Eur Heart J* 2016; 37: 2315–2381; Luft FC. *Hypertension* 2001; 37: 350–356 (1–3).  
Abbreviations: FMD, fibromuscular dysplasia; GFR, glomerular filtration rate; HT, hypertension; PPGL, pheochromocytoma/paraganglioma; RAA, renin–angiotensin–aldosterone.

According to the recommendations established by the diabetic associations, diabetes mellitus is diagnosed in such hypertensive patients when in two different measurements FPG concentration is  $\geq 7.0$  mmol/L (126 mg/dL) or plasma glucose concentration during the day is above 11.0 mmol/L (198 mg/dL). In all subjects with elevated

plasma glucose concentration, estimation of blood concentration of glycated haemoglobin (HbA1c) should be also performed (1,18).

It is well known that abnormal plasma glucose concentrations are some of the most important risk factors for cardiovascular complications in hypertensive patients (1,18).

**Table 35.4** Physical examination for secondary hypertension, organ damage and obesity

|                                                                                                                                                                                   |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Signs suggesting secondary hypertension</i>                                                                                                                                    |
| ■ Features of Cushing syndrome                                                                                                                                                    |
| ■ Skin stigmata of neurofibromatosis (pheochromocytoma)                                                                                                                           |
| ■ Palpation of enlarged kidneys (polycystic kidney)                                                                                                                               |
| ■ Auscultation of abdominal murmurs (renovascular hypertension)                                                                                                                   |
| ■ Auscultation of precordial or chest murmurs (aortic coarctation; aortic disease; upper extremity artery disease)                                                                |
| ■ Diminished and delayed femoral pulses and reduced femoral blood pressure compared to simultaneous arm BP (aortic coarctation; aortic disease; lower extremity artery disease)   |
| ■ Left-right arm BP difference (aortic coarctation; subclavian artery stenosis)                                                                                                   |
| <i>Signs of organ damage</i>                                                                                                                                                      |
| ■ Brain: motor or sensory defects                                                                                                                                                 |
| ■ Retina: fundoscopic abnormalities                                                                                                                                               |
| ■ Heart: heart rate, 3rd or 4th heart sound, heart murmurs, arrhythmias, location of apical impulse, pulmonary rales, peripheral oedema                                           |
| ■ Peripheral arteries: absence, reduction, on asymmetry of pulses, cold extremities, ischaemic skin lesions                                                                       |
| ■ Carotid arteries: systolic murmurs                                                                                                                                              |
| <i>Evidence of obesity</i>                                                                                                                                                        |
| ■ Weight and height                                                                                                                                                               |
| ■ Calculate BMI: Body weight/height <sup>2</sup> (kg/m <sup>2</sup> )                                                                                                             |
| ■ Waist circumference measured in the standing position, at a level midway between the lower border of the costal margin (the lowest rib) and uppermost border of the iliac crest |

Source: ESH/ESC 2013. Mancia G et al. *J Hypertens* 2013; 31: 1281–1357. With permission [36].

Abbreviations: BP, blood pressure; BMI, body mass index.

Elevated FPG concentration is often found in patients with secondary forms of arterial hypertension, as in hypercortisolism, pheochromocytoma or to some extent also in primary hyperaldosteronisms (1,18).

Elevated plasma glucose concentration should be also taken into the consideration when the antihypertensive therapy is planned. It is well known that some antihypertensive drugs may worsen glucose tolerance (especially thiazide or thiazide-like diuretics and beta-blockers). Therefore, these drugs should be prescribed with caution in subjects with arterial hypertension and diabetes mellitus or metabolic syndrome (1,18).

## LIPIDS

In all patients with arterial hypertension, lipid profile should be monitored. Serum concentration of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) are measured after overnight fasting, and then the low-density lipoprotein cholesterol (LDL-C) level is usually calculated using the Friedewald equation ( $LDL-C = TC - HDL-C - TG/5$ ). Results of many epidemiological studies confirm that morbidity and mortality related to cardiovascular complications is significantly

increased in hypertensive patients with elevated LDL-C concentration. In patients with arterial hypertension, it is recommended by the ESH/ESC guidelines to maintain serum LDL-C cholesterol concentration  $<100$  mg/dL ( $<2.5$  mmol/L). In patients with already existing coronary artery disease, serum LDL-C concentration should be  $<70$  mg/mL (1.8 mmol/L) and in those with the highest risk of cardiovascular complications even lower, namely  $<55$  mg/mL (1.8 mmol/L). Treatment with statins along with appropriate dietary recommendation significantly reduces cardiovascular risk in hypertensive patients; however, dose not reduce the progression of CKD (1,19).

## KIDNEY FUNCTION

Evaluation of kidney function is recommended in all patients with arterial hypertension. Serum creatinine measurement is a very convenient, cheap and easily available method; however, the results are affected by muscle mass (influenced by age, gender and racial differences in creatinine generation) as well as by high dietary protein intake. That is why serum creatinine alone is not any more accepted as an adequate marker of kidney function. As creatinine clearance measurement is very impractical

because its calculation depends on 24-h urine collection, for daily clinical practice, calculation (estimation) of creatinine clearance (eGFR) is generally accepted. Most common equations currently used are the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD) Study and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. MDRD equation is the most widely used formula in recent years. Many laboratories automatically report eGFR based on MDRD equation additionally to the creatinine measurements. CKD-EPI equation is, however, more accurate in subjects with higher eGFR levels ( $>60$  mL/min/1.73 m<sup>2</sup>). In addition, CKD-EPI may serve as a better predictor of mortality or end-stage renal disease (ESRD) than using the MDRD formula, therefore *KDIGO 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease* recommended CKD-EPI equation for GFR estimation. Measurement of serum concentration of cystatin C (low molecular weight-13 kDa-cysteine protease inhibitor, produced by all nucleated cells) is a potential alternative to measurement of serum creatinine for estimating GFR. Measurement of cystatin C is less available and more expensive than measurement of serum creatinine and therefore is not routinely used for calculation of GFR. Estimated GFR  $<60$  mL/min/1.73 m<sup>2</sup> (and repeating this value within 3 months) allocates these patients to the stage 3 or lower of the CKD classification (20–24).

Measurement of albuminuria is recommended in all patients with arterial hypertension. The frequency of urinary albumin excretion measurement depends on clinical situation and comorbidities (in patients with CKD, it should be assessed at least annually). According to the

KDIGO 2012 guideline, measurement of the albumin-to-creatinine ratio along with morning urine sample is mandatory in all patients with newly diagnosed arterial hypertension. Urinary albumin excretion in the range 30–300 mg/g creatinine is recognized as a marker of sub-clinical target-organ damage. Based on CKD classification and the rate of albuminuria, an outcome of CKD patients can be assessed (Table 35.5) (20–24).

## ELECTROLYTES

Estimation of serum sodium and potassium concentration is mandatory in each patient with newly diagnosed arterial hypertension. These results are useful in the diagnosis of secondary forms of arterial hypertension (e.g. in patients with primary hyperaldosteronism) as well as in the long-term monitoring of side effects related to the antihypertensive therapy. Detailed differential diagnosis of hypokalaemia (serum potassium concentration  $<3.5$  mmol/L) in patients with arterial hypertension is given in Figure 35.1. Hyperkalaemia (serum potassium concentration  $>5.0$  mmol/L) is usually caused by the antihypertensive therapy with direct inhibitors of the renin–angiotensin–aldosterone system (RAAS), including ACEI, ARBs or mineralocorticoid receptor antagonists, as well as indirectly by inhibiting of RAAS with blockers of the beta-adrenergic receptors. Hyperkalaemia is most frequently found in hypertensive patients with advanced CKD, diabetes mellitus, older age or treated simultaneously

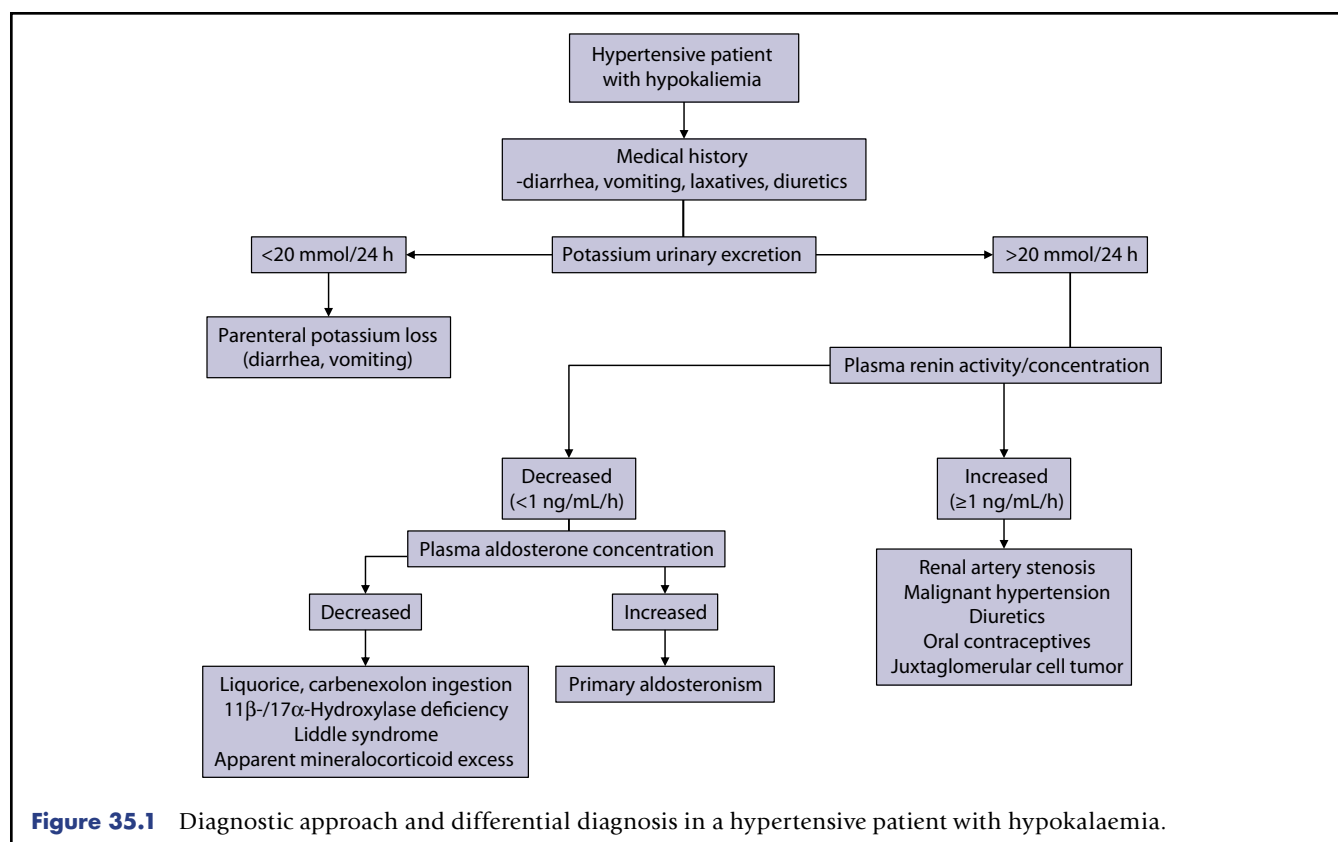
**Table 35.5** Prognosis of CKD by GFR and albuminuria category

| Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012         |     |                                  |           | Persistent albuminuria categories description and range |                             |                              |
|------------------------------------------------------------------------|-----|----------------------------------|-----------|---------------------------------------------------------|-----------------------------|------------------------------|
|                                                                        |     |                                  |           | A1                                                      | A2                          | A3                           |
|                                                                        |     |                                  |           | Normal to mildly increased                              | Moderately increased        | Severely increased           |
|                                                                        |     |                                  |           | $<30$ mg/g<br>$<3$ mg/mmol                              | 30–300 mg/g<br>3–30 mg/mmol | $>300$ mg/g<br>$>30$ mg/mmol |
| GFR categories (mL/min per 1.73 m <sup>2</sup> ) description and range | G1  | Normal or high                   | $\geq 90$ |                                                         |                             |                              |
|                                                                        | G2  | Mildly decreased                 | 60–89     |                                                         |                             |                              |
|                                                                        | G3a | Mildly to moderately decreased   | 45–59     |                                                         |                             |                              |
|                                                                        | G3b | Moderately to severely decreased | 30–44     |                                                         |                             |                              |
|                                                                        | G4  | Severely decreased               | 15–29     |                                                         |                             |                              |
|                                                                        | G5  | Kidney failure                   | $<15$     |                                                         |                             |                              |

Note: Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk.

Source: According to Levin A, Stevens PE. *Kidney Int* 2014; 85: 49–61. With permission.

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.



with two or three different inhibitors of the RAAS and/or potassium supplementation. Hyponatremia (serum sodium concentration  $<135.0$  mmol/L) in patients with arterial hypertension may be caused by the diuretic treatment (especially by the thiazide or thiazide-like diuretics). Hyponatremia is also found in patients with a malignant form of arterial hypertension as well as in hypertensive patients with heart failure or in patients with hypothyroidism. Hypernatremia (serum sodium concentration  $>145.0$  mmol/L) may be caused by primary hyperaldosteronism or by severe dehydration (6,25).

## URIC ACID

Measurement of serum uric acid (UA) concentration belongs to the list of routine laboratory tests which should be performed on each subject with arterial hypertension. It is especially important in patients with reduced kidney function (CKD stage 3–5) and/or treated with thiazide or thiazide-like as well as loop diuretics. Normal serum UA concentrations are lower in females ( $<6.0$  mg/dL =  $357$   $\mu$ mol/L) than in males ( $<7.2$  mg/dL =  $428$   $\mu$ mol/L). An increasing body of evidence suggests that asymptomatic hyperuricaemia is an independent risk factor for cardiovascular complications and CKD. The relationship between hyperuricaemia and the development of hypertension has been confirmed by several observational and experimental studies. It is also suggested that levels of serum UA can be considered as a marker of the oxidative stress associated with the activation of xanthine-oxidase, which is essential in UA production. This hypothesis opens a new interpretation of the role of serum UA in the pathogenesis of cardiovascular and renal complications. Patients whose plasma levels of UA are the

consequence of excessive production will be more prone to cardiovascular diseases compared to patients whose hyperuricaemia is caused by reduced renal excretion or increased tubular reabsorption of UA, which would predispose these patients for development of gout. Patients with hyperuricaemia who manifest gout should be treated with an aim to reduce serum UA below  $6.0$  mg/dL ( $357$   $\mu$ mol/L). This is especially important in patients with CKD and/or metabolic syndrome. It is less clear whether the asymptomatic hyperuricaemia should be treated to the same target. Recent randomised controlled trials suggested, however, a protective effect of urate-lowering therapy in preventing the progression of CKD. It seems that it is also true in reducing the risk of cardiovascular complications, but large, randomised trials are needed to prove this recommendation (26–29).

## ECG

A 12-lead electrocardiogram (ECG) is recommended in all hypertensive patients to detect left ventricular hypertrophy (LVH), left atrial dilatation, arrhythmias, or concomitant heart disease (class I, level B recommendation) (1).

Although sensitivity of ECG in detecting LVH is low, LVH detected by ECG has been found in observational studies and clinical trials to be an independent predictor of CV risk. Established ECG indices of LVH include (30–33):

- The Sokolow-Lyon index ( $SV_1 + RV_5 > 3.5$  mV)
- The modified Sokolow-Lyon index (largest S-wave + largest R-wave  $> 3.5$  mV)
- $RaVL > 1.1$  mV
- Cornell voltage QRS duration product ( $> 244$  mV\*ms)

Accordingly, ECG may also be used to detect (1):

- Patterns of ventricular overload or 'strain'
- Ischaemia
- Conduction abnormalities
- Left atrial dilatation
- Arrhythmias, including atrial fibrillation

## SCREENING EVALUATION FOR SECONDARY HYPERTENSION

Although secondary causes of hypertension can be diagnosed in a relatively small proportion of hypertensive patients, since the prevalence of hypertension is high, identifiable forms of hypertension can affect millions of patients worldwide. When correctly diagnosed and treated, patients with a secondary form of hypertension might be cured, or at least an improvement in hypertension control and a reduction of CV risk can be achieved. Although all hypertensive subjects should undergo basal workup for secondary forms of hypertension, the younger the patient and the higher and more resistant to antihypertensive therapy BP levels is present, the more thorough the pursuit for identifiable causes should be. This screening can be based on medical history, physical examination and routine laboratory investigations (Table 35.4) (1,6).

A secondary form of hypertension can be suspected in following conditions (1,34,35):

- Onset of hypertension at young age (<30 years of age, especially with no family history of hypertension)
- Severe elevation in BP (including paroxysmal rises in BP and hypertension crisis)
- Sudden onset of hypertension
- Exacerbation of previously controlled hypertension
- Poor BP response to drug therapy (resistant hypertension)
- Development of malignant hypertension
- OD inadequate to the duration of hypertension or its severity
- Diastolic hypertension developed in older subjects (age  $\geq 65$  years)
- Deterioration/worsening renal function particularly with RAAS system blockade
- Advanced hypertensive retinopathy

When a secondary form of hypertension is suspected based on basal workup, specific screening tests may become necessary, as outlined in Table 35.4. Diagnostics of secondary forms of hypertension, particularly in patients with suspicion of endocrine hypertension, should rather be performed in referral centres.

## SUMMARY

An integrated diagnostic approach to hypertensive patients in general medicine, based on comprehensive medical history, physical examination and routine tests, should aim for confirmation the diagnosis of hypertension, detection of secondary forms of hypertension, assessment of CV risk, OD and concomitant CV clinical conditions. All

hypertensive subjects should undergo basal workup for secondary forms of hypertension, but the younger the patient and the higher and more resistant to the antihypertensive therapy BP levels exist, the more thorough the pursuit for identifiable causes should be (35). In middle-aged or elderly hypertensive subjects, greater attention should be directed to the assessment of global CV risk, since those subjects are at higher risk of immediate CV events. As described in this chapter, in most patients this can be achieved by BP measurement, assessment of medical history including family history, physical examination, and routine tests. These constitute the integrated diagnostic approach in hypertensive patients, easily implanted in general medicine settings.

## REFERENCES

1. Williams B, Mancia G, Spiering W et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens* 2018; 36: 1953–2041.
2. Piepoli MF, Hoes AW, Agewall S et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016; 37: 2315–2381.
3. Luft FC. Twins in cardiovascular genetic research. *Hypertension* 2001; 37: 350–356.
4. Hunt SC, Williams RR, Barlow GK. A comparison of positive family history definitions for defining risk of future disease. *J Chronic Dis* 1986; 39: 809–821.
5. Friedman GD, Selby JV, Quesenberry CP, Jr et al. Precursors of essential hypertension: Body weight, alcohol and salt use, and parental history of hypertension. *Prev Med* 1988; 17: 387–402.
6. Kaplan NM, Victor RG. *Kaplan's Clinical Hypertension*. Wolters Kluwer: Philadelphia, 2015.
7. Julius S, Palatini P, Kjeldsen SE et al. Usefulness of heart rate to predict cardiac events in treated patients with high-risk systemic hypertension. *Am J Cardiol* 2012; 109: 685–692.
8. Benetos A, Rudnichi A, Thomas F et al. Influence of heart rate on mortality in a French population: Role of age, gender, and blood pressure. *Hypertension* 1999; 33: 44–52.
9. Lewington S, Clarke R, Qizilbash N et al. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360: 1903–1913.
10. Clark CE, Taylor RS, Shore AC et al. Association of a difference in systolic blood pressure between arms with vascular disease and mortality: A systematic review and meta-analysis. *Lancet* 2012; 379: 905–914.
11. Fedorowski A, Stavenow L, Hedblad B et al. Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals (The Malmo Preventive Project). *Eur Heart J* 2010; 31: 85–91.
12. Fagard RH, De Cort P. Orthostatic hypotension is a more robust predictor of cardiovascular events than nighttime reverse dipping in elderly. *Hypertension* 2010; 56: 56–61.
13. Vaccarino V, Holford TR, Krumholz HM. Pulse pressure and risk for myocardial infarction and heart failure in the elderly. *J Am Coll Cardiol* 2000; 36: 130–138.
14. Franklin SS. Pulse pressure as a risk factor. *Clin Exp Hypertens* 2004; 26: 645–652.
15. Nawrot TS, Staessen JA, Thijs L et al. Should pulse pressure become part of the Framingham risk score? *J Hum Hypertens* 2004; 18: 279–286.
16. Bliziotis IA, Destounis A, Stergiou GS. Home versus ambulatory and office blood pressure in predicting target organ damage in hypertension: A systematic review and meta-analysis. *J Hypertens* 2012; 30: 1289–1299.
17. Staessen JA, Thijs L, Fagard R et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients



- with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA* 1999; 282: 539–546.
18. Ryden L, Grant PJ, Anker SD et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013; 34: 3035–3087.
  19. Baigent C, Landray MJ, Reith C et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): A randomised placebo-controlled trial. *Lancet* 2011; 377: 2181–2192.
  20. Levey AS, Coresh J, Greene T et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; 145: 247–254.
  21. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013; (Suppl. 3): 1–150.
  22. Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612.
  23. Inker LA, Schmid CH, Tighiouart H et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012; 367: 20–29.
  24. Levin A, Stevens PE. Summary of KDIGO 2012 CKD Guideline: Behind the scenes, need for guidance, and a framework for moving forward. *Kidney Int* 2014; 85: 49–61.
  25. Wagner S, Metzger M, Flamant M et al. Association of plasma potassium with mortality and end-stage kidney disease in patients with chronic kidney disease under nephrologist care - The NephroTest study. *BMC Nephrol* 2017; 18: 295.
  26. Borghi C, Rosei EA, Bardin T et al. Serum uric acid and the risk of cardiovascular and renal disease. *J Hypertens* 2015; 33: 1729–1741, discussion 1741.
  27. Borghi C, Desideri G. Urate-lowering drugs and prevention of cardiovascular disease: The emerging role of xanthine oxidase inhibition. *Hypertension* 2016; 67: 496–498.
  28. Borghi C, Cicero AFG. Serum uric acid and acute coronary syndrome: Is there a role for functional markers of residual cardiovascular risk? *Int J Cardiol* 2018; 250: 62–63.
  29. Sircar D, Chatterjee S, Waikhom R et al. Efficacy of febuxostat for slowing the GFR decline in patients with CKD and asymptomatic hyperuricemia: A 6-month, double-blind, randomized, placebo-controlled trial. *Am J Kidney Dis* 2015; 66: 945–950.
  30. Levy D, Salomon M, D'Agostino RB et al. Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. *Circulation* 1994; 90: 1786–1793.
  31. Okin PM, Devereux RB, Jern S et al. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. *JAMA* 2004; 292: 2343–2349.
  32. Fagard RH, Staessen JA, Thijs L et al. Prognostic significance of electrocardiographic voltages and their serial changes in elderly with systolic hypertension. *Hypertension* 2004; 44: 459–464.
  33. Okin PM, Oikarinen L, Viitasalo M et al. Prognostic value of changes in the electrocardiographic strain pattern during antihypertensive treatment: The Losartan Intervention for End-Point Reduction in Hypertension Study (LIFE). *Circulation* 2009; 119: 1883–1891.
  34. Whelton PK, Carey RM, Aronow WS et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2017; 1: 1.
  35. Young JWF, Calhoun DA, Lenders JWM et al. Screening for endocrine hypertension: An endocrine society scientific statement. *Endocr Rev* 2017; 38: 103–122.
  36. Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1281–1357.



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# MANAGEMENT OF HYPERTENSION BY THE HYPERTENSION SPECIALIST AND THE HYPERTENSION EXCELLENCE CENTRES

# 36

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## INTRODUCTION

Before presenting the main purpose and tasks of hypertension specialists and hypertension excellence centres it is important and interesting to discuss the hypertensiology per se and contemplate whether it should be recognised as a separate discipline in medicine.

## WHAT IS HYPERTENSIOLOGY?

Hypertension is major global health burden with unfavourable increasing tendency. There are many reasons why despite broadening knowledge, improvements in understanding mechanisms and availability of potent armature, hypertension has won the title of 'number one world killer', and has kept this unwanted position for years. The gap between science, guidelines and real clinical work is obvious and broad, but as Bisognano emphasised, there is a lot that can improve blood pressure control that does not require the imprimatur of rigid national guidelines (1). He added that if we have learned anything in the 'evidence – based medicine' era, it is that we know a lot, but not everything. Furthermore, there is a great deal that could be done to improve patients' health and increase blood pressure control. Firstly, the position of hypertension as a special field of medicine should be re-examined. Does it not sound anachronistic to consider hypertension as part of nephrology, or cardiology, or angiology, or endocrinology or any other medical speciality? asked Strasser several years ago (2). However, scepticism is still present, and opponents argue, asking completely different types of questions, What justifies another medical speciality when so many hypertensives need access to a responsive informed 'primary' healthcare provider such as a general practitioner or qualified nurse practitioner? Aren't there enough cardiologists, nephrologists and endocrinologists around to deal with the very rare and difficult situations? (3). Furthermore, this debate is expanded with claims that hypertension is a disorder of blood pressure regulation, not a specific disease, and it was asked why we recognise specialists for quantitative deviation from the normal? Even more, this was flavoured with sarcasm – Isn't it like having

a specialty for fever, rather than for infectious diseases? Nevertheless, these statements on hypertension could be compared with diabetes – is diabetes not a disorder of glucose regulation? Should it not be, and aren't diabetologists capable not only of achieving glucose control but also of preventing devastating consequences of the disorder and treating various complications? Diabetes is not the only disorder of glucose regulation, nor is hypertension the only disorder of blood pressure regulation. In the twenty-first century, this should be clear to everyone who has any experience with hypertension. In fact, hypertension is a crossroads where basic science, biochemical and pharmacological research, clinical medicine and public health meet. This is the beauty of hypertension, but on the other hand, a reason why hypertension is difficult to define as a speciality. Hypertension is studied by various types of clinicians, and is a topic relevant to cardiology, neurology, endocrinology, diabetology, pharmacology, nephrology, obstetrics, paediatrics, general practice, immunology, rheumatology, interventional radiology and vascular and neurosurgery. Because of its prevalence, it is an important issue for epidemiologists and public health specialists. It is obvious that not all nephrologists, cardiologists, endocrinologists, etc. have or should have interest in hypertension. However, all the aforementioned specialists should be familiar at least with basic hypertensiology and well informed on diagnostic algorithms and treatment strategies. Those who truly have interest in hypertension should be trained in more depth in hypertensiology, becoming hypertension specialists.

As Genest said, hypertension is more than nephrology, cardiology or endocrinology, and more and more people are devoting their life to either full-time research on one of its aspects or to clinical hypertension with its multitude of patients (4). In addition, the teaching of hypertension is multidisciplinary and must be integrated as a unit and not in a 'disjointed' way, as it is so often at the present time (4). As to the existing medical specialties (i.e. cardiology or nephrology), the variety in their training programmes and differing focus of their activities does not guarantee that any one specialist will be skilled in consulting on hypertension-related problems (3). Importantly, hypertension should be an essential part of the training of general practitioners. Too many emotional, personal, family and

socioeconomic factors are involved in the clinical expression and aggravation of hypertension to be neglected, and often these factors are better handled by the family doctor than by the university specialists (4,5). Thus, the final answer to the question of whether hypertensiology is separate speciality is – yes. Several arguments favour this conclusion. Hypertension is (1) highly prevalent in the general population (the highest prevalence of chronic-noncommunicable diseases with increasing trend); (2) a major cardiovascular and cerebrovascular risk factor; (3) an established renal risk factor; (4) one of the major causes of disability; (5) a huge economic burden to all societies; (6) a complex entity where hypertension specialists should be capable of solving the most complicated cases, but also should serve as consultants in many other cases being linked among various specialities.

Thus far, hypertension is not recognised as a medical field on its own by the vast majority of governments and national physicians' chambers and is not considered a discipline *sui generis*, for example, diabetology (1–5). Until hypertension is acknowledged as a separate medical discipline, young physicians, lacking motivation and financial incentives, will be attracted by other recognised medical specialties and will be reluctant to enter the field of hypertension.

Aside from all other previously mentioned facts, stopping this brain drain from the field of hypertension (2) was one of the reasons why the European Society of Hypertension decided to start with its own programme on hypertension specialists.

## HYPERTENSION SPECIALIST PROGRAMME

### WHY DO WE NEED HYPERTENSION SPECIALISTS AND WHAT SHOULD THEY DO?

Hypertension specialists have opportunities to improve blood pressure control at global, national and local levels.

#### GLOBAL LEVEL

Hypertension is so complex that one must be aware that every hypertension specialist could not develop superb competence in all areas. Hypertension specialists represent a diverse group of board-certified physicians (7). Importantly, this group collectively must be engaged in designing, implementing, and monitoring patient-centred, evidence-based, cost-efficient best practice approaches to all levels of health protection – *primordial* (prevention of lifestyle risk factors), *primary* (prevention of vascular and target-organ damage in subjects with established risk factors), and *secondary* (prevention of recurrent events) (7). One recent example where hypertension specialists have a crucial role is an ongoing survey on blood pressure control in ESH Excellence Centres (BP-Control study in ESH Excellence Centres).

#### NATIONAL LEVEL

Hypertension specialists have opportunities to work on improvement of blood pressure control at the national level. They can develop and coordinate strategies beyond

blood pressure control which should improve health and reduce costs. Hypertension specialists have to initiate, organise and coordinate nationwide surveys on hypertension, salt intake and obesity, etc., collecting relevant recent data which should be the basis for healthcare programmes. In addition, hypertension specialists must be involved in the education of patients, nurses and physicians as well as pharmacists, who should become regular partners in the team (7). The next important task at the national level is to work on improvement of blood pressure control, bringing new knowledge and making sophisticated diagnostic methods and therapeutic procedures available and part of routine clinic work. Finally, hypertension specialists must serve as 'interplayers' between hospital physicians, general practitioners, nurses, pharmacists, health insurance companies and ministries of health and industry (pharma and food). Actions to prevent cardiovascular/renal disease should be incorporated into everyone's lives, starting in early childhood and continuing through adulthood and senescence (class IIa, level B, grade strong) (Table 36.1) (8,9).

Two groups of healthcare providers are crucial in managing hypertension at the national level – nurses and general practitioners. Nurse-coordinated prevention programmes should be well integrated into the healthcare system (class IIa, level B, grade strong) (8,9). The physician in general practice is the key person to initiate, coordinate and provide long-term follow-up. The critical task is to properly communicate with the individual patient. Hypertension specialists should be involved in plans and implementation of actions where both groups are key players. Patients with cardiac/renal disease may participate in self-help programmes to increase or maintain awareness of the need for risk factor management, for maintaining physical fitness, or for diligent self-management of therapy (class IIa, level B, grade strong) (8,9). One important task is to develop patients' educational materials which might increase their understanding and facilitate physician-patient communication. Hypertension specialists must be involved in regularly publishing patient-oriented journals which will educate patients, increasing their awareness and responsibility.

The most common barriers to guideline implementation are government or local health policy (40%), patient compliance (36%), lack of time (23%) and lack of communication (immeasurable). Hypertension specialists must work on better communication between hospital specialists

**Table 36.1** Actions to prevent cardiovascular disease

| Target group           | Action                                                                                                                                                                                                                                                                                                                                    |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| School, kindergarten   | <ul style="list-style-type: none"> <li>– Conveying the pleasures of healthy nutrition and joys of physical activity</li> <li>– Education on devastating effects of smoking and alcohol</li> </ul>                                                                                                                                         |
| Adults                 | <ul style="list-style-type: none"> <li>– Risk-adjusted prevention</li> <li>– Nurse-based activities</li> <li>– Importance of general practitioners</li> <li>– Involvement of pharmacists in the team</li> <li>– Hospital-based programme</li> <li>– Society-based programme</li> <li>– Non-personal interventions (mass media)</li> </ul> |
| Legislative activities | <ul style="list-style-type: none"> <li>– Ban smoking, reduce salt content in bread, meat products, etc.</li> </ul>                                                                                                                                                                                                                        |

and general practitioners, and they should ensure that all patients with cardiovascular/renal disease be discharged from the hospital with clear guideline-oriented treatment recommendations to minimise adverse events (class I, level B, grade strong) (8,9).

It was shown in several studies that the presence of a pharmacist improves medication adherence. Hypertension specialists should coordinate programmes which will enable pharmacists to become valuable partners in the team, starting from education to enhancing communication between pharmacists, nurses and physicians, and working on financial incentives. The main task for pharmacists should be providing education of patients on proper blood pressure measurements, a healthy lifestyle, and together with general practitioners and nurses, increasing patient and family engagement. Many hypertensive patients have multiple comorbidities with the need for complex polypharmacy regimens, thus the next task for pharmacists is to explain the need for taking so many drugs, inform patients when to take each drug, and warn them about side effects and possible interactions (7). Pharmacists should communicate with physicians and nurses, reporting to them any remark that could have impact on better blood pressure control.

Figure 36.1. presents a scheme on a network where hypertension specialists have a central role. Such care networks could enable many return visits to be organised via telemedicine, as a few minutes 'face to face' on a computer and might provide enough information to make most decisions for stable follow-up patients (1). However, in many circumstances it is more important to have in-person contact between two human beings. Again, lack of time, which is a frequent problem for physicians and nurses, could be bridged over with the help of educated pharmacists.

## LOCAL LEVEL

### GENERAL PRACTITIONER HYPERTENSION SPECIALIST

Most patients with hypertension need little investigation, and in many of them blood pressure control can be achieved by monotherapy or a two-drug regime (6,10). However, those patients should also be carefully monitored, as hypertension is a dynamic entity that can change characteristics either because of ageing and long-time duration of disease or because of developing some

secondary form of hypertension. In addition, many subjects are underdiagnosed, inadequately followed up, or undertreated. Screening programmes and education of physicians and patients should be the tasks of hypertension specialists among general practitioners.

### HOSPITAL HYPERTENSION SPECIALIST

Hypertensives with refractory hypertension, those with severe or difficult-to-control hypertension, suspicion of secondary forms of hypertension and patients who are noncompliant should be referred to a hospital hypertension specialist who has access to other experts and facilities for various laboratory and imaging investigations. Usually, hospital hypertension specialists work in ESH Excellence Centres of Hypertension. Evaluation and treatment of difficult-to-treat hypertensives, secondary forms of hypertension and resistant hypertensives are the main tasks of the hospital hypertensive specialist. The multidisciplinary approach is important as many (the majority of) patients have clusters of chronic diseases that are not efficiently addressed by disease-specific management strategies (1–7,10). For instance, patients with resistant hypertension frequently have obesity, sleep apnoea syndrome, chronic kidney disease or high salt intake; some have cognitive dysfunction or dementia, while others are noncompliant. Various hypertension specialists should be part of the team, including either interventional cardiologists or radiologists. However, they also should be involved in education of patients and be engaged in all other activities at the global and national level. Hypertension specialists must work on better communication between hospital specialists and general practitioners, and shared care should be introduced and encouraged (Figure 36.1) (6).

## WHO CAN BE A HYPERTENSION SPECIALIST?

The Hypertension Specialist Programme was organised by the European Society of Hypertension in 2000 to identify hypertension specialists in Europe, to contribute to the training of these specialists, and to improve the treatment of hypertension and thus obtain better prevention of cardiovascular and kidney diseases (11) (Figure 36.2). ESH Hypertension Specialists have to be selected from among physicians who have long-time experience, multidisciplinary knowledge and expert

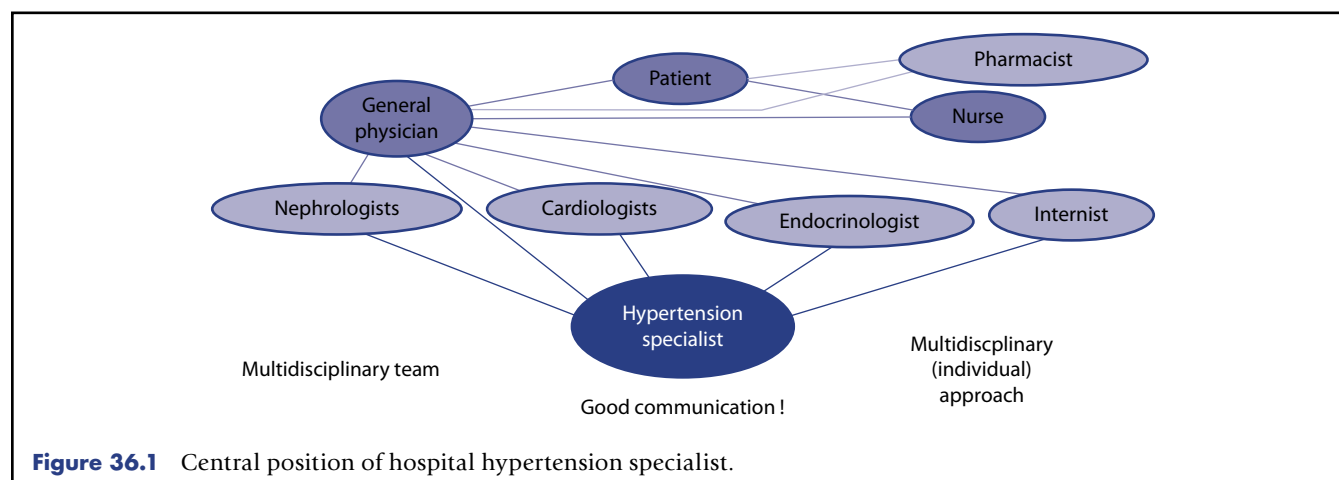


**Figure 36.1** Central position of hospital hypertension specialist.



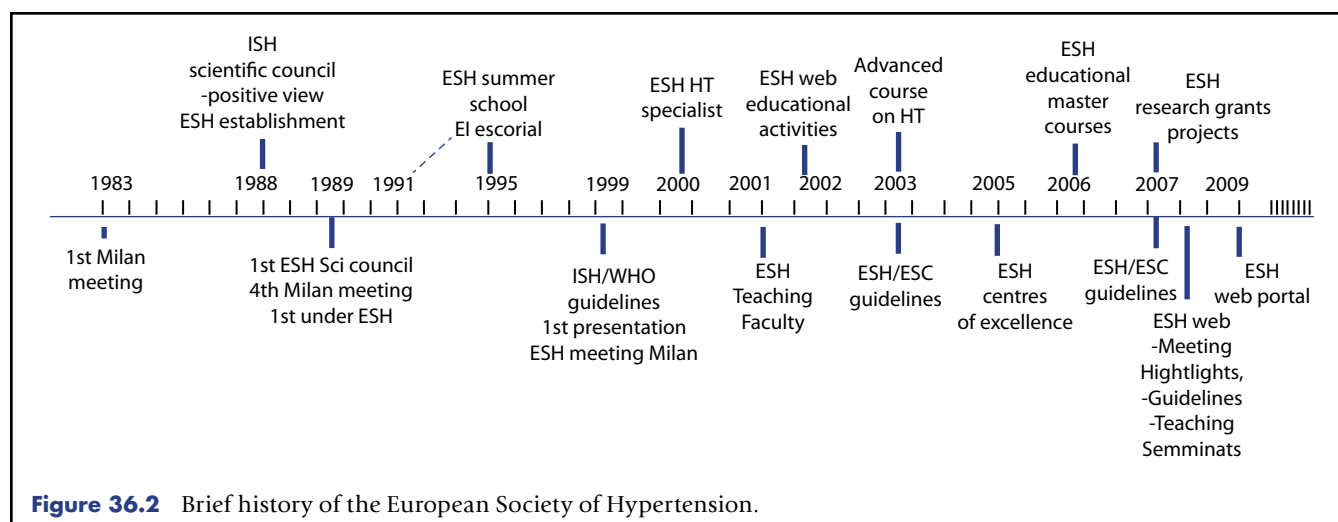


**Figure 36.2** Brief history of the European Society of Hypertension.

skills to effectively deal with complex and difficult cases of clinical hypertension and related disorders (11). The purpose of this programme is to qualify and identify practitioners who have broad knowledge of hypertension and the proven ability to apply this knowledge to the expert care of hypertensive patients (11). Eligibility criteria for recognition as a hypertension specialist of ESH are listed in Box 36.1.

Nomination is based on credits obtained through participation in scientific meetings and teaching courses endorsed by ESH (Box 36.2). Applicants should have acquired 10 credits for A and 10 credits for B. Credits must be documented and uploaded, and submitted in the online process. When describing practice activity in hypertension, an applicant should provide data on: (a) number of years of experience in the clinical management of hypertensive patients; (b) percentage of practice devoted to the care of hypertensive patients; (c) estimated number of consultations per month for hypertension-related disorders; (d) estimated number of evaluations performed per month for possible secondary hypertension assigned

to a hypertension clinic. They must describe their medical division and the entire hypertension unit/centre, and inform the ESH council of hypertension research projects/grants/fellowships in which they have been or are currently involved. Finally, each applicant is asked to describe extra hospital practice. All members in good standing and who have been a hypertension specialist for 5 years should apply for re-accreditation. Specialists should fulfil at least three of the following six criteria (required in the last 3 years): (a) participation in ESH annual meetings; (b) participation in ESH teaching activities (summer school or advanced course); (c) participation in ESH-endorsed local meetings; (d) participation in ESH distance-learning activities; (e) publication in

### BOX 36.1 ELIGIBILITY CRITERIA

1. *Conditio sine qua non*: The Hypertension Specialist should be *member of the ESH* in good standing.
2. *Clinical experience* in hypertension: At least 10 years, with particular reference to referral of patients with difficult hypertension.
3. *Training in a medical speciality* germane to hypertension (internal medicine, nephrology, cardiology, endocrinology, primary care, etc.).
4. A certain degree of *scientific activity* (e.g. publications on clinical hypertension, participation in clinical trials, etc.).
5. Continuing interest and updating in hypertension as shown by *participation in scientific meetings and membership* in hypertension-related scientific societies.
6. *Recognition* by peers at national levels.

### BOX 36.2 CREDITS NEEDED TO COLLECT FOR RECOGNITION OF THE STATUS OF HYPERTENSION SPECIALIST

| A. Scientific Meetings                                                                         | credits |
|------------------------------------------------------------------------------------------------|---------|
| Yearly ESH meetings                                                                            | 3       |
| International meetings endorsed by ESH                                                         | 2       |
| Meetings of national hypertension societies                                                    | 1       |
| B. Teaching Courses                                                                            |         |
| ESH Summer School (7 days)                                                                     | 3       |
| Teaching courses organised by national hypertension societies (minimum 2 days) endorsed by ESH | 2       |
| Teaching courses within yearly ESH meetings                                                    | 2       |
| Online programme of theoretical and practical self-assessment                                  | 2       |
| Programme endorsed by ESH                                                                      | 1       |

peer-reviewed hypertension-related journals; (f) abstracts accepted at ESH annual meeting.

The disparity between the prevalence and total burden of hypertension and the number of hypertension specialists points to a need for more hypertension specialists (6). One could argue whether better and more structured education of hypertension specialists is needed, and it has been questioned whether knowledge before and during the re-accreditation process should be verified with a comprehensive on-line test. The ESH is working on these issues. Physicians who are given the title of Hypertension Specialist should not use this title just for personal promotion by putting this diploma on their office wall. They must be aware of the highly important responsible role in patient care, population health, and cardiovascular health promotion and disease prevention.

### ESH CENTRES OF EXCELLENCE IN HYPERTENSION

In 2005 the ESH launched an initiative to create a unique Pan-European network of Hypertension Excellence Centres. The main purpose of this network is to provide a stable and organised European platform for the advancement of hypertension prevention and control (Box 36.3) (11–13). ESH Centres of Excellence consist of teams of ESH hypertension specialists based on tertiary institutions (hospitals) and are identified by their high-quality expert scientific activity in research and clinical management, including facilities to diagnose secondary hypertension (11–13). The ESH Centres of Excellence network was established to provide the highest level of both inpatient and outpatient hypertension care, including surgical and vascular interventions and assessment of global cardiovascular risk. Specific tasks are listed in Boxes 36.4 and 36.5. At the time of this writing, the total number of approved ESH Centres of Excellence is 193 (13 are associated centres). The Centres of Excellence are located in 36 European countries and the associated centres in 8 non-European countries (Argentina, Australia, Bahrain, Brazil, Israel, Lebanon, People's Republic of China and Venezuela) (Figure 36.3). The ESH Council has decided to approve applications twice a year at ESH Council meetings.

The ESH is making continuous efforts to manage the burden of hypertension in Europe by stimulating scientific exchange related to knowledge about hypertension and

#### BOX 36.3 MAIN AIM AND PURPOSE FOR THE ESH CENTRES OF EXCELLENCE

- An ESH Excellence Centre is an institution which should provide the highest level of both inpatient and outpatient hypertension care, including surgical and vascular interventions and assessment of global cardiovascular risk.
- The main purpose of the ESH Excellence Centres network is to provide a stable and organised European platform for the advancement of hypertension prevention and control.
- Multidisciplinary services must be secured.

#### BOX 36.4 SPECIFIC TASKS FOR ESH HYPERTENSION EXCELLENCE CENTRE

- To provide the best possible clinical management of patients with high blood pressure.
- To set standards in the diagnostics and treatment of hypertension in regions of service.
- To evaluate and improve blood pressure control for primary care, specialists and hypertension centres in regions of service.
- To offer continuing medical education opportunities focusing on teaching primary care physicians in the region of service.
- To carry out research (experimental/clinical/epidemiological) represented by papers in peer-reviewed international as well as local scientific journals.
- To cooperate with other ESH Hypertension Excellence Centres to increase understanding of the importance of hypertension as a major health risk in Europe.

#### BOX 36.5 GLOBAL TASKS FOR ESH CENTRES OF EXCELLENCE

1. Remain active and cooperate with the ESH Scientific Council to elaborate new hypertension control strategies in Europe.
2. Establish blood pressure clinic(s).
3. Encourage members to become ESH Hypertension Specialists.
4. Encourage members to participate in the ESH Working Groups.
5. Establish Network with other Excellence Centres (geography, problems, interest).
6. Establish Young Investigators' Network.
7. Participate in patients' record organisation (i.e. registry of fibromuscular dysplasia, atherosclerotic renovascular hypertension, adrenal tumours, obstructive sleep apnoea syndrome, renal denervation and other interventions).
8. In the framework of the hypertension specialist, to work closely with general practitioners.

supporting and building organisations committed to work for the control of hypertension (11–13).

### BLOOD PRESSURE AND VASCULAR PROTECTION (BP-VP) CLINIC

The ESH Council decided to recognise the ESH Blood Pressure-Vascular Protection Clinics (ESH BP-VP), allowing specialists running blood pressure or cardiovascular and renal risk services, but without the critical mass, to become an Excellence Centre and be plugged into this ESH framework through domicile Excellence Centre (14). ESH BP-VP Clinics consist of individuals or groups of ESH hypertension specialists working in medical practice



**Figure 36.3** Map of countries where the ESH Excellence Centres are located in Europe and the Middle East.

(primary care or institutions/hospitals) who have special interest and expertise in hypertension (14). The coordination of the interaction with these ESH BP-VP Clinics is at the Excellence Centre level. One Centre of Excellence can be associated with several ESH BP-VP Clinics with European recognition. The Centres of Excellence and the ESH BP-VP Clinics allow the organisation of a network aiming to improve the accuracy of diagnosis and management of hypertension and to be involved in multicentre clinical research activities. The main tasks are shown in Box 36.6 and the main requirements in Box 36.7 (14).

However, the final shape and structure of an ESH BP-VP Clinic may depend on the objectives, which may differ among clinics and different local healthcare systems, and may change with time. Good BP-VP Clinics may not necessarily address all the possible purposes described below. In addition to aforementioned tasks, ESH BP-VP Clinics should establish a database management system and computer software to collect, store and retrieve data in structured way with the aim to facilitate prompt monitoring implement and interpret office and out-of-office BP measurements.

**BOX 36.6 MAIN TASKS FOR THE ESH BLOOD PRESSURE AND VASCULAR PROTECTION CLINIC**

| Medical service                                                                                                                                               | Education                                                                                                    | Referral centre                                                                                            | Research                  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|---------------------------|
| <i>Integrated and coordinated</i><br>– Assessment<br>– Investigation<br>– Treatment<br>– Ongoing monitoring<br>– Auditing of therapeutic response and outcome | <i>Structural training facilities</i><br>– Doctors<br>– Nurses<br>– Other health professionals<br>– Patients | <i>Difficult patients</i><br>– Connection between GPs and Excellence Centre<br>– Facilitation of follow-up | – Recruitment of patients |

**BOX 36.7 SPECIFIC REQUIREMENTS OF AN ESH BP-VP CLINIC**

| BP measurement      | Evaluation of TOD                           | Lifestyle modification    | Follow-up monitoring   | Communication                              |
|---------------------|---------------------------------------------|---------------------------|------------------------|--------------------------------------------|
| Office unattended   | EKG<br>ECHO                                 | Integrated treatment plan | Multidisciplinary team | Patients/GPs/Nurses                        |
| ABPM                | ACR                                         |                           |                        |                                            |
| HBPM (telemedicine) | Fundoscopy<br>ABI<br>Carotid Doppler<br>PWV |                           |                        | Pharmacist ESH Excellence<br>(Shared care) |

**REFERENCES**

1. Bisognano J. Leadership message: Is all hypertension local? *J Am Soc Hypertens* 2014; 8: 778–789.
2. Strasser T. Is hypertension a medical discipline? *WHL Newsletter* 1989; (6).
3. Krakoff L. The role of the hypertension specialists. *J Hum Hypertens* 1999; 13: 151–152.
4. Genest J. Is hypertensionology a separate speciality? *WHL Newsletter* 1990; (13).
5. Beevers D. The future of hypertensionology. *WHL Newsletter* 1990; (10).
6. Beevers D. Do we need hypertensionologists? *BMJ* 1983; 287: 885–886.
7. Egan B. Opportunities for multidisciplinary ASH clinical hypertension specialists in an era of population health and accountable care: ASH leadership message. *J Am Soc Hypertens* 2014; 8: 451–456.
8. Perk J, De Backer G, Gohlke H et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012; 33: 1635–1630.
9. Mancia G, Fagard R, Narkiewicz K et al. Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1281–1357.
10. Beevers D. The role of the hypertension specialist. *J Hum Hypertens* 1998; 12: 659–661.
11. ESH Task Force. ESH hypertension specialist programme. In: Zanchetti A, Cifkova R, Parati G, Narkiewicz K (eds). *European Society of Hypertension. Past, Present and Future*. Via Medica, Gdansk; 2011: 61–67.
12. Viigimaa M, Cs F, Kjeldsen SE et al. ESH Hypertension Excellence Centres: A new strategy to combat an old foe. *European Society of Hypertension Newsletter. J Hypertens* 2007; 25: 1744–1748.
13. Farsang C, Narkiewicz K, Kiowski W et al. for the ESH Council. Excellence Centers of the European Society of Hypertension. *J of Hypertension* 2006; 24: 787.
14. Stergiou GS, Myers MG, Reid JL, Burnier M, Narkiewicz K, Viigimaaf M, Manciag G. Setting-up a blood pressure and vascular protection clinic: Requirements of the European Society of Hypertension. *J Hypertens* 2010; 28: 1780–1781.



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# Section VII

## Therapeutic Aspects

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*Stefan Engeli and Jens Jordan*

## INTRODUCTION

Non-pharmacological interventions are recommended for hypertension prevention and treatment (1–4). Given the high prevalence of hypertension and the recent discussion to lower blood pressure cutoff values for diagnosing arterial hypertension, non-pharmacological interventions may be applicable to a large number of patients. This chapter discusses commonly advocated non-pharmacological measures in hypertension prevention and management.

## WEIGHT REDUCTION

Epidemiological studies showed close associations between obesity and arterial hypertension. In NHANES III, hypertension risk increased steadily from overweight to obesity in women and men (5). The frequency of hypertension in overweight individuals aged 20–39 years was doubled compared with normal-weight participants among 1 million participants in the Community Hypertension Evaluation (6). The age-adjusted relative risk for new onset of arterial hypertension was 1.46-fold higher in overweight women and 1.75-fold higher in overweight men compared with normal-weight participants in the Framingham Heart Study (7), and this risk increased with a BMI above 23 kg/m<sup>2</sup> in African American women. Regression models corrected for the age-related rise in blood pressure demonstrated an increase in systolic blood pressure of 1 mmHg for a gain of 1.7 kg/m<sup>2</sup> and 4.5 cm waist circumference in men, or 1.3 kg/m<sup>2</sup> and 2.5 cm waist circumference in women (8). Moreover, visceral adipose tissue was strongly associated with presence of arterial hypertension in the cross-sectional Health, Ageing, and Body Composition Study, especially in individuals with low total body fat (9). Systolic blood pressure increased 3.3 mmHg per standard deviation increase of visceral adipose tissue and 2.3 mmHg per standard deviation increase in subcutaneous adipose tissue in men (10). A multivariable-adjusted linear regression analyses in another study showed that blood pressure was 1.3/1.4 mmHg higher in men per standard deviation increase in visceral adipose but not in women (11). Similarly, abdominal adiposity

more strongly affected sympathetic activity in men than in women (12). Ethnicity and genetic factors modulate the relationship between blood pressure and obesity. For example, in Pima Indians, blood pressure typically does not increase with increasing adiposity (13).

The underlying mechanisms of ‘fat-sensitive’ versus ‘fat-resistant’ blood pressure are largely unknown. Nevertheless, reducing body weight appears to be useful in ameliorating blood pressure, in reducing the number of antihypertensive medications or in preventing new onset arterial hypertension, at least in ‘fat-sensitive’ individuals. Weight loss may be particularly useful in treatment-resistant hypertensive patients, who are often obese (14). Dietary weight loss and bariatric surgery work mainly by caloric restriction, and can therefore be compared when analysing effects on blood pressure. Weight loss drugs, however, may have drug-specific effects on blood pressure. Thus, blood pressure changes with pharmacologically induced weight loss are more difficult to predict and will not be further discussed (15).

In individuals with high-normal blood pressure randomized to ‘nutritional-hygienic intervention’ or no intervention, those in the intervention group lost 2.7 kg body weight. During 5 years of follow-up, the incidence of hypertension was 8.8% in the intervention and 19.2% in the control group (16). In the larger Trials of Hypertension Prevention (TOHP) phase I (17), men and women aged 30–54 years with high-normal diastolic blood pressure were randomized to weight reduction, sodium reduction, stress management or no intervention. Individuals in the weight reduction group lost 3.9 kg weight and blood pressure decreased by 2.9/2.3 mmHg over 18 months, with a stronger reduction in severely obese patients (18). The findings were replicated in TOHP phase II (19). Individuals who lost at least 4.5 kg after 6 months and maintained their weight reduction over 30 months had the greatest decrease of blood pressure and a 0.35 relative risk for developing hypertension (20). In the Trial of Antihypertensive Interventions and Management (TAIM), overweight and obese patients with mild hypertension were randomized to nine drug/diet combination groups: placebo, 25 mg chlorthalidone, or 50 mg atenolol were combined with a usual diet, a hypocaloric diet or a low sodium/high potassium diet (21). Body weight decreased

by 4.7 kg after 6 months hypocaloric diet, and diastolic blood pressure decreased by 8.8 mmHg. In the Trial of Non-pharmacologic Interventions in the Elderly (TONE), elderly hypertensive patients on a single antihypertensive drug were randomized to reduced sodium intake, weight loss, a combination of both or usual care (22). Moderate weight loss decreased the need for antihypertensive therapy by approximately 30%.

Blood pressure-lowering effects of weight reduction achieved by dietary approaches are supported by several meta-analyses (23–25). These analyses sometimes report numbers suggesting a linear decrease of blood pressure per kg weight reduction (e.g.  $-1.1/-0.9$  mmHg/kg) (23). Calculations in that manner face several limitations (14,15,24,25): (i) blood pressure reduction is positively correlated to baseline blood pressure; (ii) effects of weight loss may be enhanced by a simultaneous increase in physical activity, moderation in alcohol intake, reduction in sodium intake and increased potassium intake (see below); (iii) the reported decrease in blood pressure is depending on the time of documentation (acute weight loss period vs. weight maintenance period when a weight loss plateau was reached); (iv) many patients are unable to maintain weight loss through lifestyle intervention in the long term; (v) considering the amount of weight lost, blood pressure reduction was less than expected in patients undergoing weight-reduction surgery.

In summary, weight loss may be considered for the prevention and management of hypertension. However, data on the long-term effects of weight loss through dietary interventions do not exist. With respect to weight reduction surgery, large weight reductions are required to modestly lower blood pressure (26), but even if weight loss is maintained for a long time, blood pressure may rise again due to increased age. This was demonstrated in the Swedish Obese Individuals (SOS) study, where weight loss decreased the risk for arterial hypertension only in the first few years after surgery (27).

## DIETARY SODIUM REDUCTION

A linear relationship between salt consumption and hypertension prevalence was suggested in the 1960s (Figure 37.1) (28). Later studies reported a more variable relationship between sodium excretion and blood pressure, most likely because of varying degrees of salt sensitivity between participants (29). However, an important relationship between blood pressure and sodium intake in treated and untreated hypertensive patients was observed (30).

In the Hypertension Prevention Trial, individuals with 78–89 mmHg diastolic blood pressure were randomly assigned to standard care or four dietary intervention groups, including reduced calories, reduced sodium, a combination of both or reduced sodium and increased potassium (31). After 3 years, mean blood pressure was reduced in all intervention groups. In THOP phase I, sodium restriction lowered blood pressure by 1.7/0.9 mmHg (32). The response to sodium restriction was less consistent in THOP phase II (20), but sodium restriction reduced hypertension incidence by 20%. In the Dietary Approach to Stop Hypertension (DASH)-sodium trial (33), participants were randomized to either

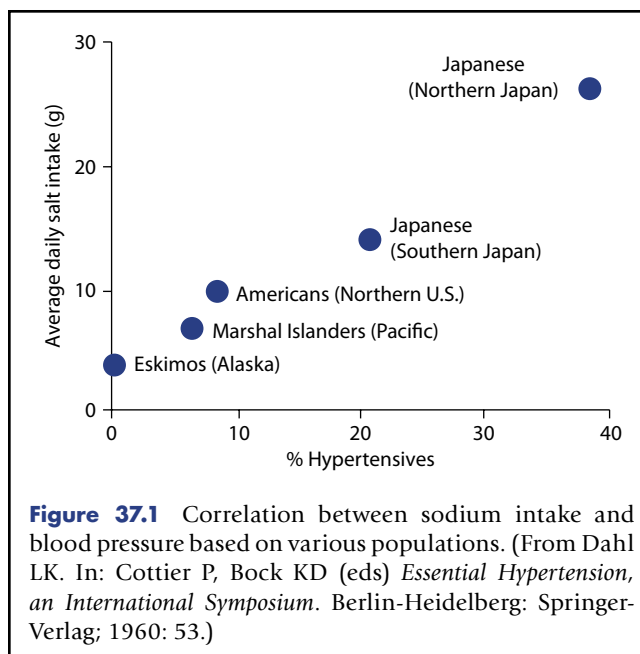


**Figure 37.1** Correlation between sodium intake and blood pressure based on various populations. (From Dahl LK. In: Cottier P, Bock KD (eds) *Essential Hypertension, an International Symposium*. Berlin-Heidelberg: Springer-Verlag; 1960: 53.)

a typical U.S. diet or the DASH diet (34). Of the participants, 41% were hypertensive. Within the assigned diet, sodium content was changed from high (150 mmol/d), to intermediate (100 mmol/d), to low (50 mmol/d) for 30 days each. In individuals assigned to the control diet, reduction of sodium intake from high to intermediate reduced systolic blood pressure by 2.1 mmHg, and a further reduction of 4.6 mmHg occurred with greater reduction of sodium intake. Diastolic blood pressure decreased in a stepwise manner, and African American and older individuals showed an even greater blood pressure response. In the TONE trial, older hypertensive patients were randomized to reduction in salt intake or no intervention (35). During a mean follow-up of 28 months, urinary sodium excretion and blood pressure were reduced by 40 mmol/day and 4.3/2.0 mmHg, respectively. With sodium restriction, more patients remained free of antihypertensive therapy.

Calculations in a meta-analysis on dietary sodium restriction provided the following results: resting blood pressure was reduced by 3.4/1.5 mmHg in the overall study population and systolic blood pressure by 4.1 mmHg in the hypertensive subpopulation. Severe sodium restriction below 2 g/d intake was slightly more effective (36). Randomized trials on sodium intake and cardiovascular outcome are missing, but cohort studies reported an increased risk of stroke, stroke mortality, and coronary heart disease mortality with increased sodium intake, whereas all-cause mortality, incident fatal and nonfatal cardiovascular disease, and coronary heart disease were not associated with increased sodium intake (36). A recent Cochrane review found the following effects of a reduction of dietary sodium intake from 200 to 66 mmol/d: no reduction in blood pressure in Caucasian normotensive individuals, but a decrease by 5.5/2.9 mmHg in hypertensive Caucasians. Blood pressure reduction in African American and Asian individuals was more pronounced, but data quality was less satisfying (37).

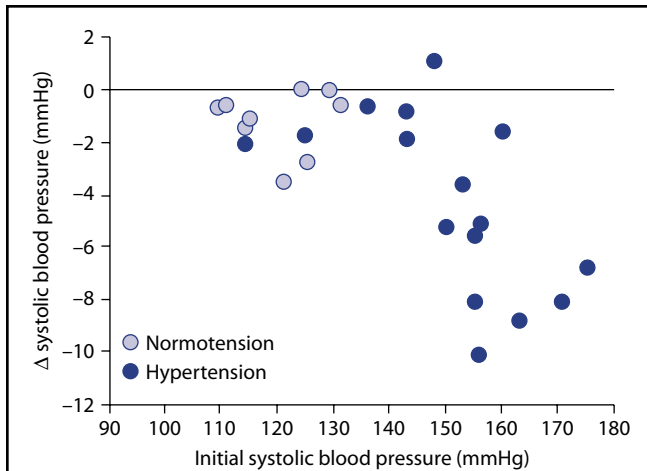


**Figure 37.2** Relationship between change of systolic blood pressure and baseline systolic blood pressure in a meta-analysis of controlled trials of reduced sodium intake and blood pressure. Hypertensive patients experienced a greater blood pressure reduction than normotensive individuals, but those with the highest baseline blood pressure remained hypertensive. (From Swales JD. *J Hum Hypertens* 1995; 9: 517–521.)

In summary, reductions in sodium intake may decrease blood pressure in normotensive and more so in hypertensive individuals (Figure 37.2). The variability in salt sensitivity and difficulties in achieving recommended salt intake of 5–6 g/d (100 mmol/d) per day in real life are important limitations. Subgroups with stronger responses, maybe older individuals, obese individuals, and African Americans, require better definition. Decreasing sodium intake inevitably increases plasma renin proportional to the degree of reduction in urinary sodium excretion (36,37). However, a follow-up study over  $\geq 13$  years observed no significant relation between plasma renin activity and coronary events, neither in normotensive individuals nor in men with hypertension (38). Based on these findings and meta-analyses (36,37), dietary sodium reduction appears to be a safe lifestyle modification (39).

### INCREASED DIETARY POTASSIUM INTAKE

In INTERSALT (29), an increase of potassium intake by 50 mmol/d reduced blood pressure by 3.6/1.9 mmHg. Blood pressure and dietary potassium were inversely correlated in large-scale surveys in the United States (40,41). The relationship was, however, attenuated after adjustment for dietary fibre and magnesium intake, whereas intervention trials did not show a consistent and sustained blood pressure reduction with potassium supplementation (42). Whether or not increased dietary potassium reduced the need for antihypertensive therapy remains controversial (43,44), but potassium supplementation may be helpful to decrease blood pressure in patients with diuretic-induced hypokalaemia (45).

The most recent meta-analyses on the relationship between potassium intake and blood pressure and

cardiovascular risk can be summarized as follows: randomized intervention trials on increased potassium intake demonstrated a blood pressure reduction of 3.5–4.5/2.0–3.0 mmHg in hypertensive patients with no significant effect in normotensive individuals. A stronger blood pressure reduction was found with substantially increased potassium intake (90–120 mmol/d). No adverse effects were found on renal function, blood lipids, or catecholamine concentrations (46). In cohort studies, potassium intake and stroke risk were inversely correlated, whereas no effects were found on coronary heart disease risk (46). Predisposing factors for a stronger response to increased potassium intake are high sodium intake, no antihypertensive treatment, and low potassium intake at baseline (47).

Based on these data, the conclusion can be drawn that dietary potassium intake of 90–120 mmol/d represents a safe measure to decrease blood pressure and stroke risk in hypertensive patients with normal renal function. Increased potassium intake is also an essential component of the DASH diet (see below). A note of caution must be made on the use of drugs blocking the renin–angiotensin–aldosterone system. The safety of increased potassium intake in this large group of hypertensive patients has not been specifically addressed in the referred studies and analyses, and must be taken into account in daily practice.

### INCREASED DIETARY CALCIUM AND MAGNESIUM INTAKE

Some epidemiological studies showed positive correlations between calcium intake or excretion and blood pressure (48,49), while others showed the opposite (41). Several meta-analyses assessed influences of calcium on blood pressure in normotensive and hypertensive individuals (50–52). One analysis calculated a reduction of 0.9/0.2 mmHg per gram of calcium intake per day (50). The effects of dietary calcium intake on blood pressure and cardiovascular risk are difficult to dissect out, because the primary sources of dietary calcium are dairy products that also include potassium, phosphorous, vitamin D and other possibly effective ingredients (53). A specific increase only in calcium intake is not recommended for hypertensive patients.

Epidemiological evidence supports a role of magnesium intake on blood pressure regulation, and increased magnesium intake was associated with reduced blood pressure and reduced hypertension incidence in individual studies (48) and in a meta-analysis (54). Interventional trials have largely failed to show a blood pressure-lowering effect of increased magnesium intake (55,56). The evidence in favour of a causal association between magnesium supplementation and blood pressure reduction is weak.

### VITAMIN SUPPLEMENTATION

An analysis of 15,317 men and women in the United States showed that vitamin A and E serum concentrations were



positively associated with blood pressure, whereas alpha- and beta-carotene were inversely associated with systolic blood pressure (57). Intervention trials failed to detect effects of vitamin E on cardiovascular outcome (58,59). A meta-analysis investigating the relationship between vitamin C intake and blood pressure in intervention trials calculated that a median dose of 500 mg/d for a median duration of 8 weeks reduces blood pressure by 3.8/2.4 mmHg in the overall population and by 4.9/2.7 mmHg in hypertensive patients (60). The potential benefit of vitamin C should be best achieved by increased intake of fresh fruits. On the other hand, the advice is not suitable for obese or diabetic patients due to the increased sugar and calorie intake associated with increased fruit intake.

Some experimental data hint at positive effects of vitamin D on blood pressure reduction, and some small studies suggest vitamin D deficiency in hypertensive patients. However, the overall amount of data on vitamin D supplementation for hypertensive patients is small and methodologically weak (61). A recent well-designed study found a significant blood pressure-reducing effect of vitamin D only in those individuals who fulfilled the criteria of vitamin D deficiency with a serum concentration <50 nmol/L at baseline (62).

### INCREASED INTAKE OF DIETARY FIBRE AND DARK COCOA

When fibre intake was <12 g/d, the relative risk of hypertension was 1.6 compared with an intake of >24 g/d in men (40). Whereas fibre intake was not related to hypertension risk in women at baseline, an inverse relationship between fibre intake and blood pressure was observed in women developing hypertension during follow-up (41). New data from a French cohort study identified a reduced hypertension risk between 16–19% for those individuals in the highest quartiles of fibre or whole grain intake (63). A meta-analysis summarized the results of 25 randomized controlled trials in which increased fibre intake was the only intervention (64). Overall, increased dietary fibre intake was associated with a non-significant 1.2/1.7 mmHg reduction in blood pressure. Clinically relevant blood pressure reductions were observed in hypertensive patients (5.9/4.2 mmHg), and in trials lasting ≥8 weeks. Because increased dietary fibre intake has additional health benefits, it can be recommended for most hypertensive patients even if blood pressure is only marginally affected.

Cocoa-rich products are associated with reduced risk of cardiovascular disease in epidemiological studies. Physiological studies on endothelial dysfunction reported that flavanols from dark cocoa increase endothelial nitric oxide production, which may reduce blood pressure. A recent meta-analysis summarised findings on 856 mostly normotensive individuals. Blood pressure reduction by flavanol-rich cocoa products was 2.8/2.2 mmHg. Whereas trial duration generally was short, blood pressure reducing effects were only seen in trials of 2-week duration (65). Given the short duration of trials, and because some studies tested an obesogenic amount of >100 g cocoa, regular intake of dark cocoa or chocolate cannot be recommended. Promises of cocoa-rich studies and shortcomings of cocoa studies in the cardiovascular field have been recently reviewed (66).

### SPECIFIC DIETS: VEGETARIAN, VEGAN, MEDITERRANEAN, DASH

Vegetarian diets are characterized by high intake of fibre, calcium, potassium, magnesium, polyunsaturated and monounsaturated fatty acids and low, or in case of a strictly vegan diet, absent intake of animal protein and saturated fats. Compared with non-vegetarians, vegetarians and vegans tend to have lower blood pressure and lower incidence of arterial hypertension (67), and red meat intake increased the risk of incident hypertension in a French cohort (63). The differences in age-adjusted blood pressure between meat eaters and vegans were 4.2/2.8 mmHg in men and 2.6/1.7 mmHg in women, but the difference was largely due to differences in BMI (67). Adherence to a vegetarian or vegan diet decreased the risk for new-onset hypertension and moderately decreased blood pressure in individuals with high-normal or increased blood pressure (68,69). More recent statements suggest that a vegetarian diet is not harmful and may be beneficial also for hypertensive individuals when supply of certain micronutrients is ensured (70).

The traditional Mediterranean diet is characterized by a high intake of vegetables, fruits, nuts, cereals, and a high intake of olive oil but a low intake of saturated lipids. The diet also includes moderately high intake of fish, a low-to-moderate intake of dairy products (mostly in the form of cheese or yogurt), and low intake of meat and poultry. Regular but moderate alcohol quantities are ingested, primarily in the form of red wine. Adherence to this type of diet has been associated with lower total mortality (71,72) and reduced complications after myocardial infarction (73). Blood pressure reduction may contribute to cardiovascular benefit (74). In an interventional trial, patients assigned to 3 months of a Mediterranean diet showed a 6/7 mmHg reduction compared to patients assigned the low-fat diet (75). The PREDIMED cardiovascular prevention study reported a substantial reduction of cardiovascular events with Mediterranean diets that was especially true in hypertensive patients (76). Another trial compared a Mediterranean diet with diets reduced in carbohydrates or fat to study weight loss. Besides the well-documented weight reduction, the reduction in blood pressure with all diets was the best predictor of increased eGFR over 2 years of intervention (77). In summary, Mediterranean diets are safe and can clearly be recommended for hypertensive patients.

The DASH trial was designed as an 11-week dieting program in 459 patients with mild, untreated hypertension. Individuals were randomly assigned to one of three diets for an 8-week intervention period. All meals were prepared by a research kitchen (78). The nutrient composition of the control diet represented a typical American diet. The fruit-and-vegetable diet was rich in potassium and fibre but otherwise similar to the control diet. The DASH diet was rich in fruits, vegetables and low-fat dairy products with reduced saturated and total fat (for details: <http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/index.htm>). The sodium content of each diet was similar at approximately 3 g/d. Weight and alcohol intake were kept constant. The DASH diet lowered blood pressure by 6/3 mmHg, while the fruit-and-vegetable diet lowered blood pressure by 3/1 mmHg. The blood pressure effect

of the DASH diet was more pronounced in hypertensive patients and in African Americans. Efficacy of the DASH diet has been confirmed in subsequent studies (63,79); thus the DASH diet can be recommended for hypertensive patients.

### REDUCED ALCOHOL CONSUMPTION AND SMOKING CESSATION

Cross-sectional studies documented increased blood pressure and hypertension risk with higher levels of alcohol intake (80). In a large survey of 30,000 individuals, blood pressure increased by 0.9/0.6 mmHg per daily drink in men and 2/1 mmHg in women who consumed two or more drinks (81). A J-shaped association between alcohol intake and blood pressure was reported by some but not all studies (82). Moderation of alcohol consumption reduced blood pressure in normotensive men (83). In heavy drinkers with hypertension, the reduction of alcohol consumption reduced blood pressure by 14/7 mmHg at two 2 years' follow-up, while no changes occurred in the control group (84). In another randomized trial, however, a reduction from 432 to 230 g alcohol per week for 6 months decreased blood pressure only by 2/2 mmHg (85). Two meta-analyses calculated that a reduction of alcohol consumption may reduce blood pressure by approximately 4/2 mmHg (49,86). In summary, moderation in alcohol intake to two drinks per day in men and one to two drinks per day in women is a sensible recommendation for hypertensive patients.

Smoking increases the relative risks for coronary heart disease in hypertensive individuals with low or high cholesterol levels by 3.0 and 9.7 in men and 2.3 and 15.9 in women, respectively (87). Some studies suggested that chronic smokers have similar blood pressure (88), and in the case of light smokers even lower blood pressure than nonsmokers (89). However, the finding that daytime ambulatory blood pressure was increased in smokers whereas office blood pressure was similar in smokers and nonsmokers may explain the earlier findings (90). Furthermore, smoking may diminish the response to antihypertensive therapy (91), thus smoking cessation should be recommended in all patients. Besides the possible positive role on blood pressure and blood pressure treatment, the reduction of cardiovascular risk through smoking cessation speaks for itself (92,93). However, nicotine is highly addictive, and therefore simple advice to stop smoking rarely suffices. Behavioural interventions, nicotine replacement therapy or other pharmacological smoking cessation aids may be considered.

### EXERCISE

A large body of epidemiological studies demonstrated that physical fitness is associated with reduced cardiovascular morbidity and mortality. Multimodal interventions integrating physical exercise are included in recent European guidelines on cardiovascular disease prevention (94). While earlier recommendations often focused on aerobic exercise, now the specific benefits of endurance and strengthening exercises are recognized. Depending on

cardiovascular risk, it may be prudent to conduct exercise stress testing before commencing a training program, and to gradually increase exercise intensity and duration over time.

In hypertensive individuals, endurance training on a bike three or seven times per week at 70% maximum work capacity for 1 month each reduced blood pressure by 11/9 and 16/11 mmHg, respectively (95). More moderate levels of exercise, for example, walking, may also be effective (96,97). In a meta-analysis of 72 trials in which exercise was the only intervention, blood pressure decreased on average by 3/2 mmHg in the overall population and by 7/5 mmHg in hypertensive patients (98). A meta-analysis that included several forms of exercise protocols found a blood pressure reduction of 3.5/2.5 mmHg with endurance training, 1.8/3.2 mmHg with dynamic resistance training, and 10.9/6.2 mmHg with isometric resistance training (99). A meta-analysis of studies assessing antihypertensive responses to dynamic resistance training showed that blood pressure decreased at least as much as with aerobic exercise training. Greater blood pressure reductions occurred in individuals with higher resting blood pressure, approximately 6/5 mmHg in hypertensives and 3/3 mmHg in individuals with prehypertension, and in non-white individuals (100). Blood pressure reduction with endurance training and with dynamic resistance training is greater in hypertensive patients compared with normotensive individuals (100). However, a recent meta-analysis in young adults with prehypertension and hypertension suggested that guideline-recommended exercise interventions may have a transient blood pressure-lowering effect that may not be sustained in the longer term (101).

In patients with treatment-resistant arterial hypertension, treadmill training for 8–12 weeks reduced systolic and diastolic daytime ambulatory blood pressure by 6/12 and 3/7 mmHg, respectively (102). The result is of special interest because these patients are at particularly high cardiovascular risk. In summary, increased levels of physical activity reduce blood pressure and cardiovascular mortality in hypertensive patients (103). Exercise intensity and the exact type of exercise need to be tailored to the ability of the patient and require individualized counselling.

### CONCLUSIONS

There is abundant evidence that lifestyle changes and dietary measures are effective to prevent the development of hypertension and reduce blood pressure in hypertensive patients. Figure 37.3 summarizes the most commonly recommended non-pharmacological measures. Additional measures such as relaxation methods and others are on the horizon but are less well characterized than those described in this chapter (4). Lifestyle modification counselling should be offered to all patients with or at risk of hypertension, and particularly in those with additional cardiovascular risk factors. The main challenge remains the optimal implementation of such lifestyle strategies. Apart from advice from healthcare professionals, government legislation and regulation as well as societal change will be necessary to aid patients in choosing and sustaining healthy lifestyle decisions.

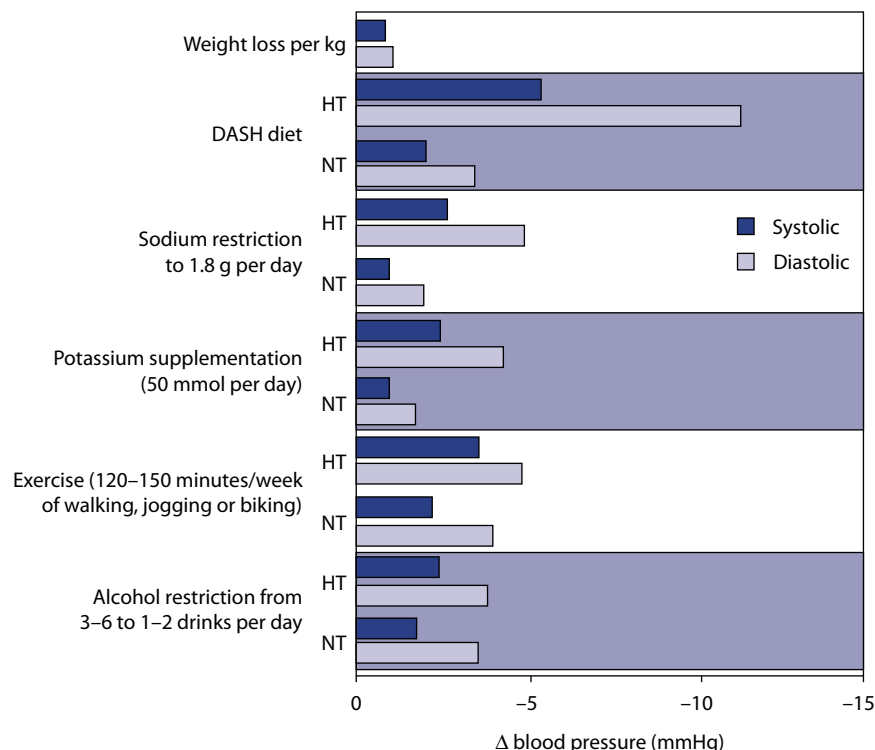


**Figure 37.3** Estimates of blood pressure-lowering effects of commonly recommended non-pharmacological interventions. The results are based upon the data presented in this chapter. It should be recognized, though, that blood pressure-lowering effects of combinations of these measures are not necessarily additive.

## REFERENCES

- Appel LJ, Giles TD, Black HR et al. ASH position paper: Dietary approaches to lower blood pressure. *J Am Soc Hypertens* 2010; 4: 79–89.
- Hackam DG, Quinn RR, Ravani P et al. Canadian Hypertension Education Program. The 2013 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol* 2013; 29: 528–542.
- ESH/ESC Task Force for the Management of Arterial Hypertension. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1925–1938.
- Brook RD, Appel LJ, Rubenfire M et al. Beyond medication and diet: Alternative approaches to lowering blood pressure. A scientific statement from the American Heart Association. *Hypertension* 2013; 61: 1360–1383.
- Must A, Spadano J, Coakley EH et al. The disease burden associated with overweight and obesity. *JAMA* 1999; 282: 1523–1529.
- Stamler R, Stamler J, Riedlinger WF et al. Weight and blood pressure. Findings in hypertension screening of 1 million Americans. *JAMA* 1978; 240: 1607–1610.
- Wilson PW, D'Agostino RB, Sullivan L et al. Overweight and obesity as determinants of cardiovascular risk: The Framingham experience. *Arch Intern Med* 2002; 162: 1867–1872.
- Doll S, Paccaud F, Bovet P et al. Body mass index, abdominal adiposity and blood pressure: consistency of their association across developing and developed countries. *Int J Obes Relat Metab Disord* 2002; 26: 48–57.
- Ding J, Visser M, Kritchevsky SB et al. The association of regional fat depots with hypertension in older persons of white and African American ethnicity. *Am J Hypertens* 2004; 17: 971–976.
- Fox CS, Massaro JM, Hoffmann U et al. Abdominal visceral and subcutaneous adipose tissue compartments: Association with metabolic risk factors in the Framingham Heart Study. *Circulation* 2007; 116: 39–48.
- Liu J, Fox CS, Hickson DA et al. Impact of abdominal visceral and subcutaneous adipose tissue on cardiometabolic risk factors: The Jackson Heart Study. *J Clin Endocrinol Metab* 2010; 95: 5419–5426.
- Tank J, Heusser K, Diedrich A et al. Influences of gender on the interaction between sympathetic nerve traffic and central adiposity. *J Clin Endocrinol Metab* 2008; 93: 4974–4978.
- Weyer C, Pratley RE, Snitker S et al. Ethnic differences in insulinemia and sympathetic tone as links between obesity and blood pressure. *Hypertension* 2000; 36: 531–537.
- Jordan J, Yumuk V, Schlaich M et al. Joint statement of the European Association for the Study of Obesity and the European Society of Hypertension: Obesity and difficult to treat arterial hypertension. *J Hypertens* 2012; 30: 1047–1055.
- Jordan J, Schlaich M, Redon J et al. For the European Society of Hypertension Working Group on Obesity and the Australian and New Zealand Obesity Society. Obesity drugs and cardiovascular outcomes. *J Hypertens* 2011; 29: 189–193.
- Stamler R, Stamler J, Gosch FC et al. Primary prevention of hypertension by nutritional-hygienic means. Final report of a randomized, controlled trial. *JAMA* 1989; 262: 1801–1807.
- The Trials of Hypertension Prevention Collaborative Research Group. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, phase I. *JAMA* 1992; 267: 1213–1220.
- Stevens VJ, Corrigan SA, Obarzanek E et al. Weight loss intervention in phase 1 of the Trials of Hypertension Prevention. The TOHP Collaborative Research Group. *Arch Intern Med* 1993; 153: 849–858.
- The Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, phase II. *Arch Intern Med* 1997; 157: 657–667.
- Stevens VJ, Obarzanek E, Cook NR et al. Long-term weight loss and changes in blood pressure: Results of the Trials of Hypertension Prevention, phase II. *Ann Intern Med* 2001; 134: 1–11.

21. Langford HG, Davis BR, Blaufox D et al. Effect of drug and diet treatment of mild hypertension on diastolic blood pressure. The TAIM Research Group. *Hypertension* 1991; 17: 210–217.
22. Whelton PK, Appel LJ, Espeland MA et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: A randomized controlled Trial of Nonpharmacologic Interventions in the Elderly (TONE). *JAMA* 1998; 279: 839–846.
23. Neter JE, Stam BE, Kok FJ et al. Influence of weight reduction on blood pressure: A meta-analysis of randomized controlled trials. *Hypertension* 2003; 42: 878–884.
24. Aucott L, Poobalan A, Smith WC et al. Effects of weight loss in overweight/obese individuals and long-term hypertension outcomes: A systematic review. *Hypertension* 2005; 45: 1035–1041.
25. Semlitsch T, Jeitler K, Berghold A et al. Long-term effects of weight-reducing diets in people with hypertension. *Cochrane Database Syst Rev* 2 March 2016; 3: CD008274.
26. Sjöström L, Lindroos AK, Peltonen M et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004; 351: 2683–2693.
27. Sjöström CD, Lystig T, Lindroos AK. Impact of weight change, secular trends and ageing on cardiovascular risk factors: 10-year experiences from the SOS study. *Int J Obes (Lond)* 2011; 35: 1413–1420.
28. Dahl LK. Possible role of salt intake in the development of essential hypertension. In: Cottier P, Bock KD (eds) *Essential Hypertension, an International Symposium*. Berlin-Heidelberg: Springer-Verlag; 1960: 53.
29. Intersalt Cooperative Research Group. Intersalt: An international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *BMJ* 1988; 297: 319–328.
30. Stamler J, Caggiula A, Grandits GA et al. Relationship to blood pressure of combinations of dietary macronutrients. Findings of the Multiple Risk Factor Intervention Trial (MRFIT). *Circulation* 1996; 94: 2417–2423.
31. Hypertension Prevention Trial Research Group. The Hypertension Prevention Trial: three-year effects of dietary changes on blood pressure. *Arch Intern Med* 1990; 150: 153–162.
32. He J, Whelton PK, Appel LJ et al. Long-term effects of weight loss and dietary sodium reduction on incidence of hypertension. *Hypertension* 2000; 35: 544–549.
33. Sacks FM, Svetkey LP, Vollmer WM et al. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. *N Engl J Med* 2001; 344: 3–10.
34. Appel LJ, Moore TJ, Obarzanek E et al. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* 1997; 336: 1117–1124.
35. Appel LJ, Espeland MA, Easter L et al. Effects of reduced sodium intake on hypertension control in older individuals: results from the Trial of Nonpharmacologic Interventions in the Elderly (TONE). *Arch Intern Med* 2001; 161: 685–693.
36. Aburto NJ, Ziolkovska A, Hooper L et al. Effect of lower sodium intake on health: systematic review and meta-analyses. *BMJ* 2013; 346: f1326.
37. Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. *Cochrane Database Syst Rev* 9 Nov 2017; (11): CD004022.
38. Meade TW, Cooper JA, Peart WS. Plasma renin activity and ischemic heart disease. *N Engl J Med* 1993; 329: 616–f1619.
39. Swales JD. Salt and blood pressure revisited. *J Hum Hypertens* 1995; 9: 517–521.
40. Ascherio A, Rimm EB, Giovannucci EL et al. A prospective study of nutritional factors and hypertension among US men. *Circulation* 1992; 86: 1475–1484.
41. Ascherio A, Hennekens C, Willett WC et al. Prospective study of nutritional factors, blood pressure, and hypertension among US women. *Hypertension* 1996; 27: 1065–1072.
42. Whelton PK, Buring J, Borhani NO et al. The effect of potassium supplementation in persons with a high-normal blood pressure. Results from phase I of the Trials of Hypertension Prevention (TOHP). *Ann Epidemiol* 1995; 5: 85–95.
43. Siani A, Strazzullo P, Giacco A et al. Increasing the dietary potassium intake reduces the need for antihypertensive medication. *Ann Intern Med* 1991; 115: 753–759.
44. Jr GR, Neaton JD, Elmer PJ et al. The influence of oral potassium chloride on blood pressure in hypertensive men on a low-sodium diet. *N Engl J Med* 1990; 322: 569–574.
45. Kaplan NM, Carnegie A, Raskin P et al. Potassium supplementation in hypertensive patients with diuretic-induced hypokalemia. *N Engl J Med* 1985; 312: 746–749.
46. Aburto NJ, Hanson S, Gutierrez H et al. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. *BMJ* 2013; 346: f1378.
47. Filippini T, Violi F, D'Amico R, Vinceti M. The effect of potassium supplementation on blood pressure in hypertensive individuals: A systematic review and meta-analysis. *Int J Cardiol* 2017; 230: 127–f1135.
48. Staessen J, Fagard R, Lijnen P, Amery A. A population study on the relationship between blood pressure and the excretion of urinary cations. *J Cardiovasc Pharmacol* 1984; 6(Suppl 1): S210–S214.
49. Stamler J, Liu K, Kj R et al. Eight-year blood pressure change in middle-aged men: relationship to multiple nutrients. *Hypertension* 2002; 39: 1000–1006.
50. Griffith LE, Guyatt GH, Cook RJ et al. The influence of dietary and nondietary calcium supplementation on blood pressure: an updated meta-analysis of randomized controlled trials. *Am J Hypertens* 1999; 12: 84–92.
51. Dickinson HO, Nicolson DJ, Cook JV et al. Calcium supplementation for the management of primary hypertension in adults. *Cochrane Database Syst Rev* 19 April 2006; (2): CD004639.
52. Cormick G, Ciapponi A, Cafferata ML, Belizán JM. Calcium supplementation for prevention of primary hypertension. *Cochrane Database Syst Rev* 30 June 2015; (6): CD010037.
53. McGrane MM, Essery E, Obbagy J et al. Dairy consumption, blood pressure, and risk of hypertension: an evidence-based review of recent literature. *Curr Cardiovasc Risk Rep* 2011; 5: 287–298.
54. Mizushima S, Cappuccio FP, Nichols R, Elliott P. Dietary magnesium intake and blood pressure: A qualitative overview of the observational studies. *J Hum Hypertens* 1998; 12: 447–453.
55. Whelton PK, Kumanyika SK, Cook NR et al. Efficacy of non-pharmacologic interventions in adults with high-normal blood pressure: results from phase 1 of the Trials of Hypertension Prevention. *Am J Clin Nutr* 1997; 65: 652S–660S.
56. Dickinson HO, Nicolson DJ, Campbell F et al. Magnesium supplementation for the management of essential hypertension in adults. *Cochrane Database Syst Rev* 19 July 2006; (3): CD004640.
57. Chen J, He J, Hamm L et al. Serum antioxidant vitamins and blood pressure in the United States population. *Hypertension* 2002; 40: 810–816.
58. Lee IM, Cook NR, Gaziano JM et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: A randomized controlled trial. *JAMA* 2005; 294: 56–65.
59. Lonn E, Yusuf S, Hoogwerf B et al. Effects of vitamin E on cardiovascular and microvascular outcomes in high-risk patients with diabetes: results of the HOPE study and MICRO-HOPE substudy. *Diabetes Care* 2002; 25: 1919–1927.
60. Juraschek SP, Guallar E, Appel LJ, Miller ER3rd. Effects of vitamin C supplementation on blood pressure: A meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2012; 95: 1079–1088.
61. Wuerzner G, Burnier M, Waeber B. Should hypertensive patients take vitamin D? *Curr Hypertens Rep* 2012; 14: 318–323.
62. Sluyter JD, Camargo CA Jr, Stewart AW et al. Effect of monthly, high-dose, long-term Vitamin D supplementation on central blood pressure parameters: A randomized controlled trial sub-study. *J Am Heart Assoc* 2017; 6: e006802.
63. Lelong H, Blacher J, Baudry J et al. Individual and combined effects of dietary factors on risk of incident hypertension: Prospective analysis from the NutriNet-Santé cohort. *Hypertension* 2017; 70: 712–720.
64. Whelton SP, Hyre AD, Pedersen B et al. Effect of dietary fiber intake on blood pressure: A meta-analysis of randomized, controlled clinical trials. *J Hypertens* 2005; 23: 475–481.
65. Ried K, Sullivan TR, Fakler P et al. Effect of cocoa on blood pressure. *Cochrane Database Syst Rev* 15 August 2012; (8): CD008893.
66. Aprotosoaie AC, Miron A, Trifan A et al. The cardiovascular effects of cocoa polyphenols - an overview. *Diseases* 2016; 4: E39.
67. Appleby PN, Davey GK, Key TJ. Hypertension and blood pressure among meat eaters, fish eaters, vegetarians and vegans in EPIC-Oxford. *Public Health Nutr* 2002; 5: 645–654.
68. Rouse IL, Beilin LJ, Armstrong BK, Vandongen R. Blood-pressure-lowering effect of a vegetarian diet: controlled trial in normotensive individuals. *Lancet* 1983; 1: 5–10.
69. Margetts BM, Beilin LJ, Vandongen R, Armstrong BK. Vegetarian diet in mild hypertension: A randomised controlled trial. *BMJ* 1986; 293: 1468–1471.
70. Craig WJ, Mangels AR. Position of the American Dietetic Association: vegetarian diets. *J Am Diet Assoc* 2009; 109: 1266–1282.



71. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* 2003; 348: 2599–2608.
72. Knuops KT, de Groot LC, Kromhout D et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. *JAMA* 2004; 292: 1433–1439.
73. de Lorgeril M, Salen P, Martin JL et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* 1999; 99: 779–985.
74. Psaltopoulou T, Naska A, Orfanos P et al. Olive oil, the Mediterranean diet, and arterial blood pressure: the Greek European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Am J Clin Nutr* 2004; 80: 1012–1018.
75. Estruch R, Martinez-Gonzalez MA, Corella D et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: A randomized trial. *Ann Intern Med* 2006; 145: 1–11.
76. Estruch R, Ros E, Salas-Salvadó J et al. PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013; 368: 1279–1290.
77. Tirosh A, Golan R, Harman-Boehm I et al. Renal function following three distinct weight loss dietary strategies during 2 years of randomized controlled trial. *Diabetes Care* 2013; 36: 2225–2232.
78. Appel LJ, Moore TJ, Obarzanek E et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* 1997; 336: 1117–1124.
79. Miller ER3rd, Erlinger TP, Appel LJ. The effects of macronutrients on blood pressure and lipids: an overview of the DASH and OmniHeart trials. *Curr Atheroscler Rep* 2006; 8: 460–465.
80. MacMahon SW, Blackett RB, Macdonald GJ, Hall W. Obesity, alcohol consumption and blood pressure in Australian men and women. The National Heart Foundation of Australia Risk Factor Prevalence Study. *J Hypertens* 1984; 2: 85–91.
81. van Leer EM, Seidell JC, Kromhout D. Differences in the association between alcohol consumption and blood pressure by age, gender, and smoking. *Epidemiology* 1994; 5: 576–582.
82. Gillman MW, Cook NR, Evans DA et al. Relationship of alcohol intake with blood pressure in young adults. *Hypertension* 1995; 25: 1106–1110.
83. Puddey IB, Beilin LJ, Vandongen R, Rouse IL. A randomized controlled trial of the effect of alcohol consumption on blood pressure. *Clin Exp Pharmacol Physiol* 1985; 12: 257–261.
84. Lang T, Nicaud V, Darne B, Rueff B. Improving hypertension control among excessive alcohol drinkers: A randomised controlled trial in France. The WALPA Group. *J Epidemiol Commun Health* 1995; 49: 610–616.
85. Cushman WC, Cutler JA, Hanna E et al. Prevention and Treatment of Hypertension Study (PATHS): effects of an alcohol treatment program on blood pressure. *Arch Intern Med* 1998; 158: 1197–1207.
86. Xin X, He J, Frontini MG et al. Effects of alcohol reduction on blood pressure: A meta-analysis of randomized controlled trials. *Hypertension* 2001; 38: 1112–1117.
87. Houterman S, Verschuren WM, Kromhout D. Smoking, blood pressure and serum cholesterol-effects on 20-year mortality. *Epidemiology* 2003; 14: 24–29.
88. Fogari R, Zoppi A, Lusardi P et al. Cigarette smoking and blood pressure in a worker population: A cross-sectional study. *J Cardiovasc Risk* 1996; 3: 55–59.
89. Primates P, Falaschetti E, Gupta S et al. Association between smoking and blood pressure: evidence from the health survey for England. *Hypertension* 2001; 37: 187–193.
90. Mann SJ, James GD, Wang RS, Pickering TG. Elevation of ambulatory systolic blood pressure in hypertensive smokers. A case-control study. *JAMA* 1991; 265: 2226–2228.
91. Materson BJ, Reda D, Freis ED, Henderson WG. Cigarette smoking interferes with treatment of hypertension. *Arch Intern Med* 1988; 148: 2116–2119.
92. Rosenberg L, Kaufman DW, Helmrach SP, Shapiro S. The risk of myocardial infarction after quitting smoking in men under 55 years of age. *N Engl J Med* 1985; 313: 1511–1514.
93. Rosenberg L, Palmer JR, Shapiro S. Decline in the risk of myocardial infarction among women who stop smoking. *N Engl J Med* 1990; 322: 213–217.
94. Piepoli MF, Hoes AW, Agewall S et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis* 2016; 252: 207–274.
95. Nelson L, Jennings GL, Esler MD, Korner PI. Effect of changing levels of physical activity on blood-pressure and haemodynamics in essential hypertension. *Lancet* 1986; 2: 473–476.
96. Kingwell BA, Jennings GL. Effects of walking and other exercise programs upon blood pressure in normal individuals. *Med J Aust* 1993; 158: 234–238.
97. Kelley GA, Kelley KS, Tran ZV. Walking and resting blood pressure in adults: A meta-analysis. *Prev Med* 2001; 33: 120–127.
98. Fagard RH. Exercise is good for your blood pressure: effects of endurance training and resistance training. *Clin Exp Pharmacol Physiol* 2006; 33: 853–856.
99. Cornelissen VA, Smart NA. Exercise training for blood pressure: A systematic review and meta-analysis. *J Am Heart Assoc* 2013; 2: e004473.
100. MacDonald HV, Johnson BT, Huedo-Medina TB et al. Dynamic resistance training as stand-alone antihypertensive lifestyle therapy: A Meta-Analysis. *J Am Heart Assoc* 2016; 5: e003231.
101. Williamson W, Foster C, Reid H et al. Will exercise advice be sufficient for treatment of young adults with prehypertension and hypertension? A systematic review and meta-analysis. *Hypertension* 2016; 68: 78–87.
102. Dimeo F, Pagonas N, Seibert F et al. Aerobic exercise reduces blood pressure in resistant hypertension. *Hypertension* 2012; 60: 653–638.
103. Rossi A, Dikareva A, Bacon SL, Daskalopoulou SS. The impact of physical activity on mortality in patients with high blood pressure: A systematic review. *J Hypertens* 2012; 30: 1277–1288.



# THE PROTECTIVE CARDIOVASCULAR EFFECTS OF ANTIHYPERTENSIVE TREATMENT

# 38

Alberto Zanchetti (Late)\* and Costas Thomopoulos

## INTRODUCTION

Therapy of hypertension was undoubtedly one of the major achievements of medicine during the second half of the twentieth century. This is not only because pharmacological agents capable of reducing blood pressure have been successfully developed starting from the 1950s, but also because the effects of drug-induced blood pressure lowering have rigorously been tested by means of the best evidence-providing approach, large randomized controlled trials (RCTs). Indeed, hypertension experts can be proud that antihypertensive therapy has been the first among cardiovascular therapies, long before therapies of myocardial infarction and chronic heart failure, that has been tested by this approach, using so-called 'hard' endpoints; that is, outcomes that can be easily diagnosed and the diagnosis of which can be easily verified. The need of solid evidence in favour of therapeutic lowering of blood pressure was particularly impelling because prejudice prevailing among clinicians and investigators until the mid-twentieth century was that 'hypertension may be an important compensatory mechanism, which should not be tampered with, even were it certain we could control it' (1). This prejudice was, so to say, a heritage of the old ontological concept of medicine, by which changes in body functions were simply compensatory mechanisms to preserve some other functions of the body – in the case of hypertension, to preserve perfusion of vital organs, especially the kidney. Hence, the term 'essential' by which arterial hypertension has long been baptized, as was fever in the eighteenth century, on the basis of the same ontological interpretation of its beneficial compensatory action: 'la fièvre essentielle est une affection de la vie qui s'efforce d'éloigner la mort' (essential fever is an affection of life that endeavors to postpone death) (2). Still, in 1957, an author wrote in *The Lancet* 'Even in the case of true arterial hypertension neither product of test-tube or crucible halts, nor delays materially, the unfavourable course of the disease' (3).

## SHOULD HYPERTENSION BE TREATED? THE SUCCESSFUL STORY OF BLOOD PRESSURE LOWERING

Seen retrospectively, the prejudice was a happy one, because soon after the first effective blood pressure-lowering drugs became available around 1950, a series of brilliant controlled therapeutic trials were initiated to test whether blood pressure lowering by drugs was accompanied by greater benefit than harm. The first study was not randomized, and active or no treatments were assigned alternatively, but starting in 1966, the results of randomized placebo-controlled trials began to be published, using hard outcomes, such as stroke, myocardial infarction and mortality.

In a systematic survey we completed in 2014 (4) we have identified 68 randomized controlled trials with a total of 245,885 patients (1,058,177 patient-years) in which blood pressure-lowering drugs have been compared to placebo (or no treatment) or more-intense has been compared to less-intense blood pressure lowering in cohorts of hypertensive patients (or of predominantly hypertensive patients). As summarized in [Figure 38.1](#), all considered outcomes were significantly reduced by blood pressure lowering, with the risk of stroke and heart failure being reduced to the greatest extent (36% and 38%, respectively, for a standardized systolic/diastolic blood pressure difference between active and control groups of 10/5 mmHg), but also risks of coronary heart disease events and cardiovascular and all-cause death were significantly reduced, though to a lesser extent (20%, 16% and 10%, respectively). These risk reductions are remarkably similar to those provided by the 1994 meta-analysis by Collins and MacMahon (5), including only 17 trials on 47,653 patients, and this indicates that the beneficial effects of antihypertensive treatment have not been substantially reduced by the large simultaneous prescription of lipid-lowering and antiplatelet agents in

\* Professor Alberto Zanchetti died in March 2018, after sending his chapter in collaboration with Dr. Thomopoulos. His contribution to the whole series of the ESH books on hypertension has been outstanding. He will be sadly missed by his colleagues and friends.

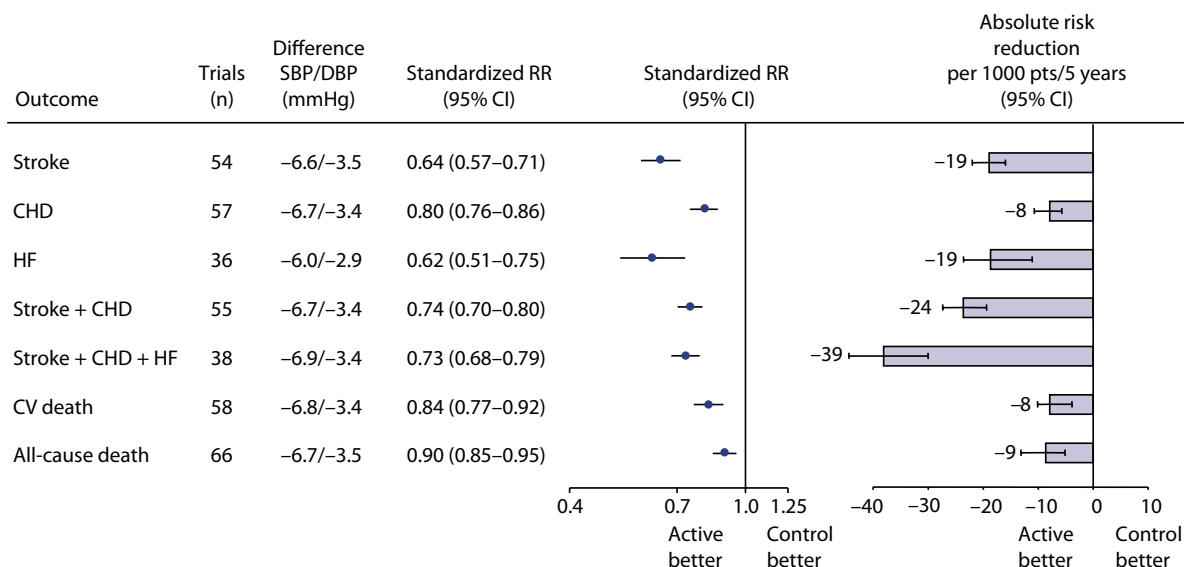


**Figure 38.1** Relative and absolute risk reduction of various outcomes in trials of blood pressure lowering. Analysis including intentional and non-intentional trials exclusively in hypertensive patients. *Abbreviations:* CHD, coronary heart disease; CI, confidence intervals; CV, cardiovascular; DBP, diastolic blood pressure; HF, heart failure; n, number; NNT, number needed to treat; pts, patients; RR, Mantel-Haenszel risk ratios; SBP, systolic blood pressure. Standardized RR is to an SBP/DBP reduction of 10/5 mmHg. The column Absolute Risk Reduction reports number (and 95% CI) of events prevented every 1000 patients treated for 5 years with a standardized RR. NNT are numbers (and 95% CI) of patients needed to treat for 5 years to prevent one event. (From data in Thomopoulos C et al. *J Hypertens* 2014; 32: 2285-2295.)

contemporary medicine. Meta-regression analyses have also shown that the risks of stroke, heart failure and cardiovascular death are related in a semi-logarithmic way to the extent of the systolic, diastolic and pulse pressure reductions, without a preference for any of these blood pressures (Figure 38.2) (4).

## INITIATION OF ANTIHYPERTENSIVE TREATMENT

Despite the overwhelming evidence of the benefits of blood pressure-lowering treatment, trial-based evidence about the systolic blood pressure threshold at which treatment should be initiated is weak. The 2013 ESH-ESC guidelines (6) give a strong recommendation (class I, level A) to promptly initiate antihypertensive drug treatment 'in individuals with grade 2 and 3 hypertension with any level of cardiovascular risk', but advise to consider 'initiation of antihypertensive drug therapy in grade 1 hypertensive patients at low to moderate risk only when blood pressure is within this range at several repeated visits or elevated by ambulatory blood pressure criteria, and remains within this range despite a reasonable period with lifestyle measures' (6). Despite all these precautions, this recommendation is classified only as class IIa (conflicting evidence and/or divergence of opinion) and level of evidence B.

The issue about the poor level of evidence favouring active blood pressure lowering in individuals with systolic blood pressure (SBP)/diastolic blood pressure (DBP) values within what is usually defined grade 1 (or stage 1) hypertension (SBP 140-159 mmHg and/or DBP 90-99

mmHg) was first raised in 2009 (7), when we called attention to the fact that the few trials conducted in the 1970s-1980s to what was then defined as 'mild' hypertension could not be taken as reliable evidence supporting treatment of grade 1 hypertension, as patients included in the 'mild' hypertension trials had been recruited on the basis of DBP values only (often in a range much wider than the 90-99 mmHg range now used for grade 1 hypertension). Furthermore, in most of the 'mild' hypertension trials SBP was not considered among recruitment criteria, and in some of them SBP could be as high as 200 mmHg.

In 2012, a Cochrane collaboration tried to overcome this difficulty by making an individual patient meta-analysis of the 'mild' hypertension trials including only data from those patients whose blood pressure values were in the grade 1 range (8). This meta-analysis was unable to show a significant reduction in the risk of any cardiovascular outcome alone or in combination. Although based on a small number of patients and events (e.g. only 30 strokes) these negative results were widely publicized as warning against overtreating grade 1 hypertension, and obviously influenced the cautious attitude all guidelines had when discussing management of grade 1 hypertension.

Since 2013, new analyses of available data have been conducted. The Blood Pressure-Lowering Treatment Trialists' Collaboration (BPLTTC) made an attempt to increase the number of patients and events by including other individuals from other trials with baseline SBP/DBP in the grade 1 range (9). This extended meta-analysis showed significant reductions in stroke, major cardiovascular events, cardiovascular and all-cause mortality. The BPLTTC conclusions, however, were limited by the fact that about 50% of the added individuals were already

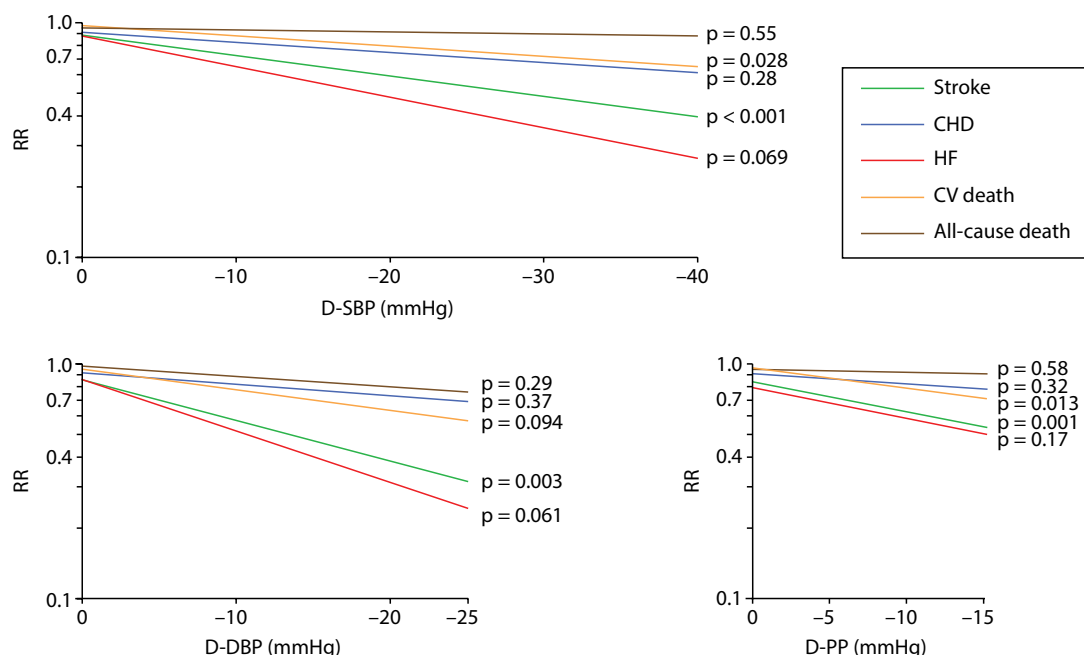


**Figure 38.2** Relationships of outcome reductions to the extent of blood pressure reductions. Metaregressions of risk ratios on absolute blood pressure differences (active treatment group minus placebo or less active treatment group) in 47 trials of intentional blood pressure lowering. Regressions relative to stroke are in green; CHD in blue; HF in red; CV death in orange; All-cause death in brown. Abbreviations: CHD, coronary heart disease event; CV, cardiovascular; D-DBP, diastolic blood pressure difference; D-PP, pulse pressure difference; D-SBP, systolic blood pressure difference; HF, heart failure; RR, Mantel-Haenszel risk ratios. (From Thomopoulos C et al. *J Hypertens* 2014; 32: 2285–2295, by courtesy of *Journal of Hypertension*.)

under some blood pressure-lowering treatment at baseline, and therefore could not be correctly defined as grade 1 hypertensive patients. Furthermore, most of the individuals added were diabetic, with the consequence that the total cardiovascular risk in the placebo group of the BPLTTC meta-analysis (6.2% cardiovascular death in 10 years) was beyond the limits of low-moderate risk (which normally is <5%).

Another, more powerful meta-analytical approach has recently been followed by our group. Among all blood pressure-lowering trials, we have chosen those in which patients had been randomized in absence of current treatment, in order to avoid incorrectly labelling hypertension grade. We identified 32 trials (including 104,359 patients) that could be classified as investigating grade 1, 2 or 3 hypertension on the basis of the average baseline blood pressure in each trial (10). Significant reductions of the risk of all major cardiovascular outcomes were found to be induced by blood pressure lowering at all grades of hypertension with no trend toward different relative risk reductions at different hypertension grades. In particular, six trials in 16,036 individuals were classified as on grade 1 hypertension, and their meta-analysis showed significant reductions in the risk of stroke, coronary events, the composite of stroke and coronary events, cardiovascular and all-cause deaths (Figure 38.3a). As some of these trials included patients at high cardiovascular risk, another meta-analysis was done only including trials or trial subgroups with mean baseline SBP/DBP values in the grade 1 range and a low to moderate cardiovascular risk (<5% cardiovascular death in 10 years in the control

groups). Also, in the 8975 patients of this meta-analysis, blood pressure-lowering treatment significantly decreased the risk of stroke, coronary events, the composite of stroke and coronary events and all-cause death (Figure 38.3b). Absolute risk reduction was large, amounting to 21 strokes, 34 major cardiovascular events and 19 deaths prevented every 1000 patients treated for 5 years (10).

The results of this meta-analysis (10) have been further supported by the recently published results of the Heart Outcomes Prevention Evaluation (HOPE)-3 trial (11), which has shown a significant 27% reduction of major cardiovascular outcomes in patients at an intermediate level of cardiovascular risk with baseline SBP values higher than 143.5 mmHg (mean 154 mmHg).

On the whole, despite the absence of a large randomized placebo-controlled trial specifically investigating blood pressure-lowering treatment in patients with grade 1 hypertension at low to moderate cardiovascular risk, the data of our meta-analysis (10) and the results of the HOPE-3 subgroup analysis (11) provide a much stronger evidence-based support in favour of initiating active drug treatment in grade 1 low-moderate risk hypertensives (12) than the arguments that could be used in the 2013 ESH-ESC guidelines (6).

A related question is whether there is evidence supporting initiation of antihypertensive treatment in individuals with blood pressure values in the range defined as high-normal or pre-hypertension (SBP 120–139 mmHg, DBP 80–90 mmHg), and whether a decision should depend on the level of their cardiovascular risk. We have recently

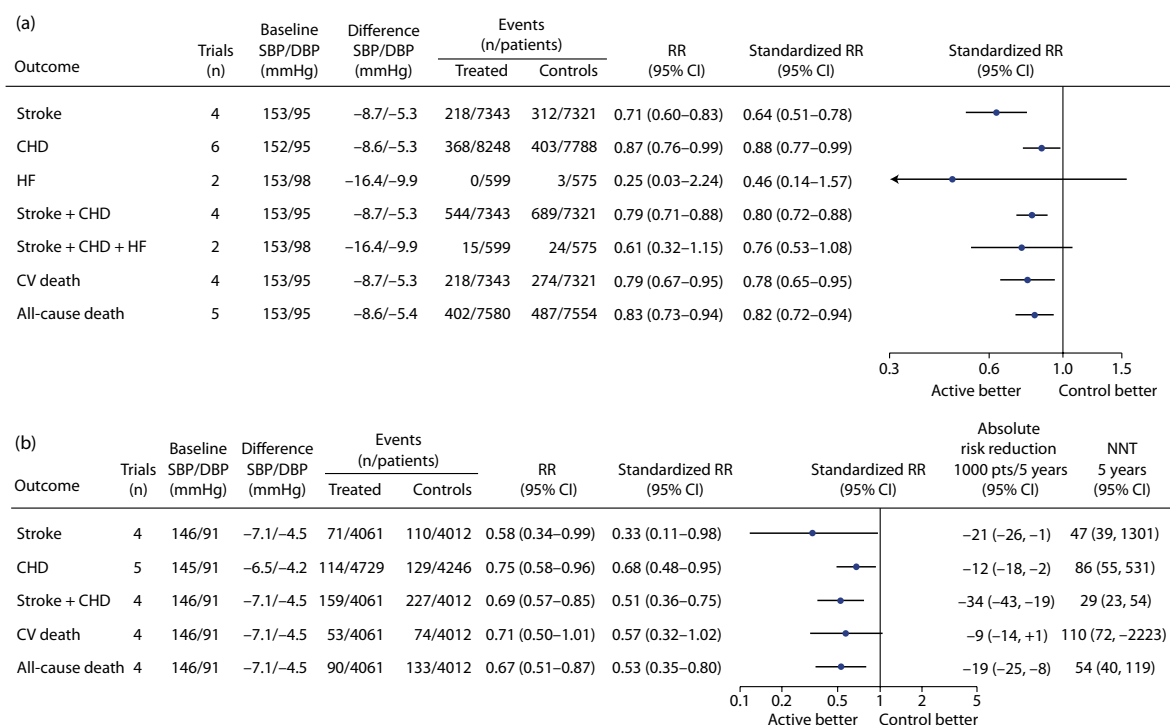


**Figure 38.3** Effects of blood pressure lowering in trials of grade 1 hypertension. Meta-analyses of trials in which average baseline SBP/DBP were in the range 140–159/90–99 mmHg (all trials without or minimal baseline antihypertensive drugs at randomization). (a) All grade 1 trials independent of total cardiovascular risk. (b) Only grade 1 trials or trial subgroups at low-moderate risk. Abbreviations: CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; RR, risk ratios. Standardized RR is to an SBP/DBP difference of 10/5 mmHg. (From Thomopoulos C et al. *J Hypertens* 2014; 32: 2296–2304, by courtesy of *Journal of Hypertension*.)

identified 24 randomized controlled trials providing data on 47,991 individuals with high-normal or normal blood pressure in absence of baseline treatment. When these trials were stratified according to total cardiovascular risk, no significant benefits were found in those including individuals at low-moderate risk (less than 5% cardiovascular mortality in 10 years), whereas a significant reduction in stroke risk was found in those trials including individuals at high-very high cardiovascular risk, mostly because of symptomatic cardiovascular disease (13) (Figure 38.4). In conclusion, only individuals with symptomatic cardiovascular disease should consider blood pressure-lowering treatment when their blood pressure is in the high-normal and normal range.

## BLOOD PRESSURE TREATMENT TARGETS

Although the target values to which blood pressure should be brought by drug treatment to optimize treatment benefits is of prominent interest for the patients and the treating physician, it is surprising that, among the large number of antihypertensive treatment trials (as many as 72), so few (only 14) have compared the effects of more versus less intense blood pressure-lowering treatment, and even less have investigated precise SBP or DBP targets.

When we first reviewed the subject in 2009 (7), we showed that the recommendation frequent in guidelines current at the time (14,15), namely, to lower SBP to less

than 130 mmHg in high cardiovascular risk patients (e.g. post-stroke or post-myocardial infarction) and in hypertensives with diabetes, was unsupported by trial evidence or supported by controversial evidence. As a consequence, the 2013 ESH-ESC guidelines (6) recommended a SBP target of less than 140 mmHg in most groups of hypertensive patients (those at low-moderate cardiovascular risk, those with diabetes, those with previous stroke or transient ischaemic attack, those with coronary heart disease, those with diabetic or nondiabetic chronic renal disease), though with a different class of recommendation and a different level of available evidence (6).

Since 2013 new data and new analyses have become available. In 2014 we published a meta-analysis of 32 blood pressure-lowering trials (including 128,232 individuals), showing that risk of all outcomes could be significantly reduced when SBP in the treated group was lowered to mean values less than 150 mmHg and compared to SBP values above 150 mmHg in the control group, and when it was lowered to mean values less than 140 mmHg in the treated group and compared to values above 140 mmHg in the control group. However, when SBP values below were compared to SBP above the cutoff of 130 mmHg, only stroke and all-cause death were significantly reduced (10).

In November 2015, the results of a large National Institutes of Health (NIH)-sponsored trial comparing a SBP goal of less than 120 mmHg with the usual goal of less than 140 mmHg were published (16). The Systolic Blood Pressure Intervention Trial (SPRINT) was stopped

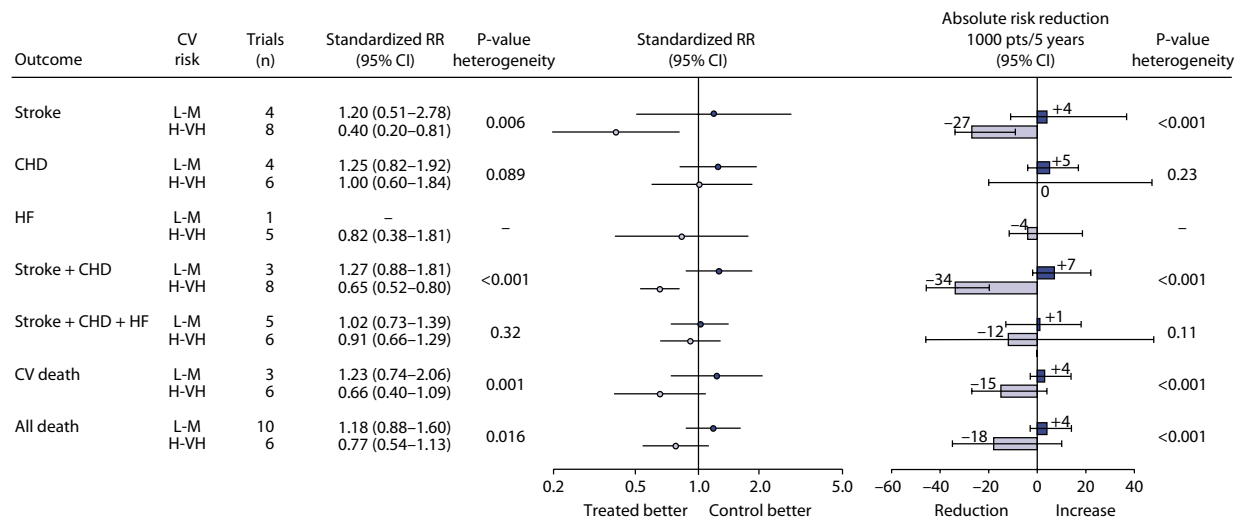


**Figure 38.4** Relative risk and absolute risk reduction of various morbidity and mortality outcomes in individuals with high-normal or normal blood pressure: Comparison of individuals at low-moderate (L-M) and high-very high (H-VH) cardiovascular risk. Risk ratios (RR) are standardized to an SBP/DBP difference of 10/5 mmHg. Rectangles at the right represent absolute risk reductions expressed as number (and 95% confidence intervals) of events prevented every 1000 individuals treated for 5 years with a standardized RR. P-values for heterogeneity refer to differences in standardized risk ratios and, respectively, absolute risk reductions between individuals at low-moderate versus high-very high cardiovascular risk. Abbreviations: CHD, coronary heart disease; CV, cardiovascular; DBP, diastolic blood pressure; HF, heart failure; H-VH, high-very high; L-M, low-moderate; n, number; pts, patients; RR, risk ratio; SBP, systolic blood pressure. (From Thomopoulos C et al. *J Hypertens* 2017; 35: 2150–2160, by courtesy of *Journal of Hypertension*.)

early because of a significant reduction of the primary endpoint in the group with more intense blood pressure-lowering treatment. The results of SPRINT have been received with obvious interest but have also raised some perplexities. Among the latter, it has been found surprising that stroke, the cardiovascular outcome known to be most sensitive to blood pressure decrease, was not significantly reduced in SPRINT. The most important benefit of the lower blood pressure goal in SPRINT was a marked reduction in heart failure risk, which may have resulted from a larger use of diuretics and renin–angiotensin system blockers in the group with lower blood pressure (17). The point has also been raised that the blood pressure measurements in SPRINT may hardly be comparable with those used in other trials (as well as in current medical practice), because in SPRINT blood pressure was measured by an automatic device in absence of a doctor or nurse, and the reported values were likely lower than those to be expected by the use of conventional office blood pressure (18).

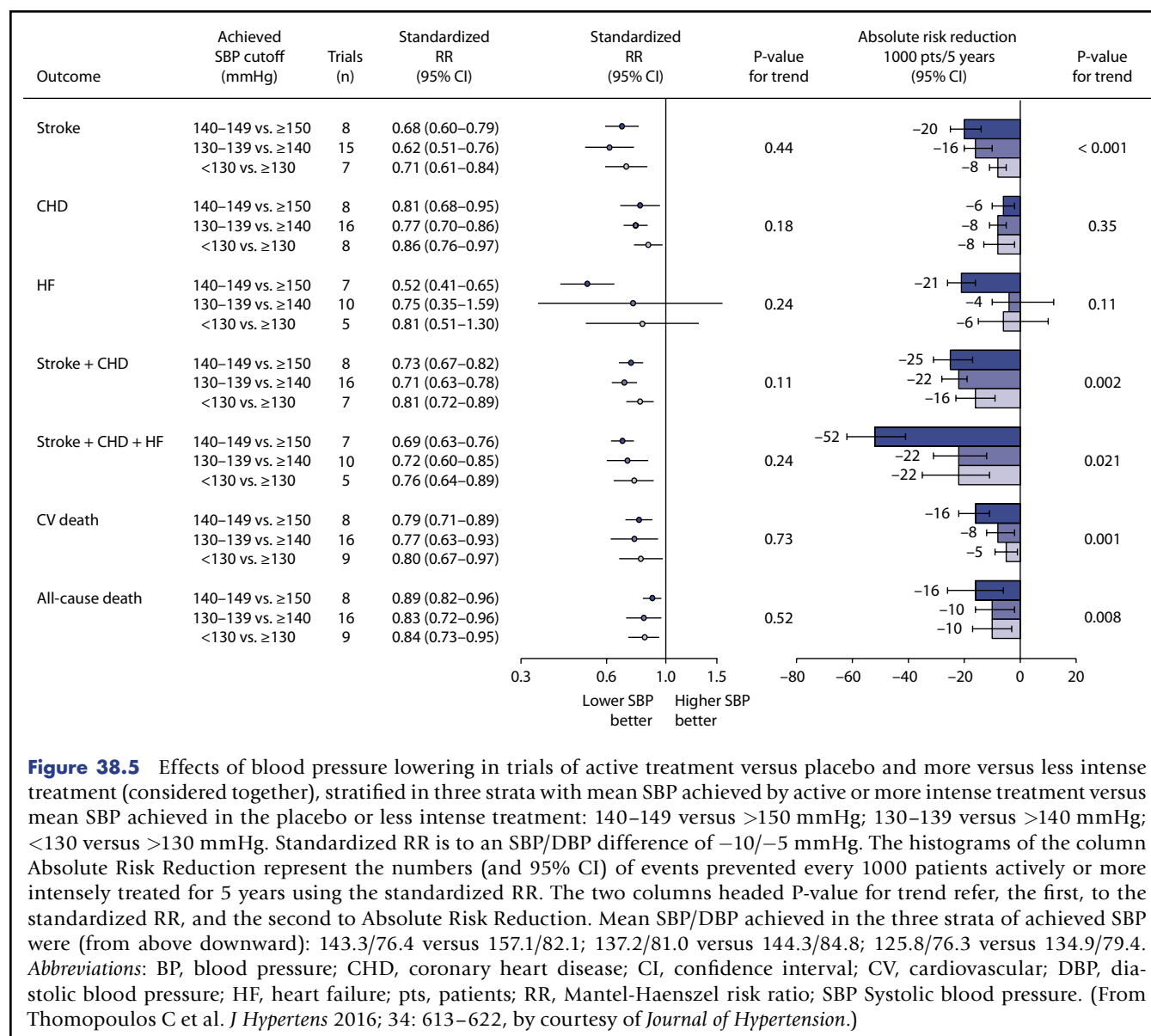
After the publication of SPRINT, we have updated our meta-analysis of blood pressure-lowering trials stratified according to the three different cutoffs of achieved SBP (below and above 150, 140 and 130 mmHg). The meta-analysis now includes 35 trials on 138,452 individuals and shows (Figure 38.5) that lowering SBP below 130 mmHg can significantly reduce most types of outcomes (stroke, coronary events, cardiovascular and all-cause death); however, absolute outcome reduction was definitely smaller than at higher SBP cutoffs (19), and permanent treatment discontinuations for adverse events were significantly greater (20). It should be emphasized, however, that even for SBP values less than 130 mmHg mean risk estimates of

all outcomes were lower than 1, hence there was no indication of a J-shaped relationship of the risk of any major outcome with achieved SBP, at least down to values several mmHg below 130.

Since the publication of the 2013 ESH-ESC guidelines, our meta-analyses have also provided further evidence on the DBP target: both meta-analyses of trials in which achieved mean DBP values were below 90 mmHg in the actively treated group and above 90 mmHg in the control group, and below and above 80 mmHg showed significant reductions of all major outcomes (10,19). Admittedly, in trials in which DBP achieved values below (vs. above) 80 mmHg, SBP also achieved significantly lower values in the active versus placebo treatment groups, and it is therefore difficult to ascribe the benefit of morbidity and mortality risk reduction to the lower DBP rather than to the lower SBP. In any case, our meta-analyses (10,19) show that DBP values several mmHg lower than 80 mmHg are at least safe, being associated with a reduction rather than an increase in cardiovascular risk.

In conclusion, the recommendations given in 2013 by all major guidelines (6,21) to achieve SBP and DBP targets lower than 140 and, respectively, 90 mmHg can be placed now, thanks to new meta-analyses, on much firmer ground, and therefore with a greater strength. The additional recommendation can now be given that achieving SBP values lower than 130 mmHg and DBP values lower than 80 mmHg appears safe and can be associated with some further benefit, provided addition of drugs or dose increase are not incrementing adverse events and consequently the risk of permanent treatment discontinuation (20). Whether these recommendations are valid for all phenotypes of





hypertension, and particularly in the elderly or in secondary prevention, remains to be ascertained by further studies, such as the ongoing Stroke in Hypertension Optimal Treatment (SHOT) trial (17), and further analyses.

### ARE THERE CLINICALLY RELEVANT DIFFERENCES IN THE PROTECTIVE CARDIOVASCULAR EFFECTS OF DIFFERENT CLASSES OF ANTIHYPERTENSIVE DRUGS?

There are a number of pharmacologically different classes of blood pressure-lowering drugs that, because of this property, have been widely used in treating arterial hypertension. The existence of multiple classes and their discovery and introduction into therapeutic usage at different times have often stimulated experts at developing and discussing ranks or orders of choice or step-care systems, based sometimes on

drug costs (older drugs are commonly cheaper than newer ones) or on the assumption of specific protective properties of some agents independent of the blood pressure-lowering action or on the frequency of adverse effects, and different recommendations have been given in different guidelines.

However, there have been a very large number of randomised controlled trials (RCTs) comparing the effects on fatal and nonfatal cardiovascular events of different classes of antihypertensive agents between themselves or with placebo, and we have recently completed and published three different sets of meta-analyses that help doctors in making informed decisions (22). The body of evidence available consists of (i) 55 RCTs comparing in 195,267 individuals the effects on cardiovascular events of each of the five major classes of antihypertensive drugs (diuretics, beta-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers) versus placebo (23); (ii) 50 RCTs directly (head-to-head) comparing the cardiovascular disease risk of at least two different classes of drugs (24); and (iii) 38

of the placebo-controlled RCTs and 37 of the head-to-head comparative RCTs providing data on treatment-induced adverse events leading to permanent treatment discontinuation (25).

The results of these large meta-analyses are summarized in a qualitative but easy-to-understand way in Figure 38.6. Each major class of blood pressure-lowering drugs, when compared to placebo, is able to significantly reduce the risk of stroke and major cardiovascular events (23) and when compared head-to-head to other drug classes has comparable effects on major cardiovascular events considered together and on cardiovascular and all-cause death, but some differences are found in the prevention of cause-specific effects: in particular, diuretics appear to prevent the risk of heart failure better than the other classes, beta-blockers to reduce less effectively the risk of stroke, calcium antagonists to prevent the risk of stroke better and the risk of heart failure less than other classes, the ACE inhibitors to prevent stroke risk less and coronary heart disease risk better than other drugs, and angiotensin receptor blockers are slightly less effective than other classes in coronary risk prevention (24). On the whole, Figure 38.6 clearly shows that similarities between the effects of the various classes on antihypertensive agents are largely preponderant over small differences.

Figure 38.6 also shows that, when compared to placebo, the reduction in cardiovascular risk obtained by each class of antihypertensive agents is accompanied by an increase in adverse events leading to treatment discontinuation, with the only exception of angiotensin receptor blockers (discontinuation non-significantly different from placebo) and, when directly compared between themselves, all classes have similar effects on major cardiovascular events, but angiotensin receptor blockers are accompanied by significantly fewer discontinuations due to adverse events (25).

### DO PATIENTS' CHARACTERISTICS OR ACCOMPANYING CONDITIONS MAKE A CLASS OF ANTIHYPERTENSIVE AGENTS PREFERABLE IN SOME GROUPS OF PATIENTS?

There is no evidence from RCTs that the various classes of antihypertensive drugs differ in their capacity to reduce cardiovascular risk according to age (26) or sex (27) (except for caution in using renin–angiotensin system blockers in women with childbearing potential because of possible teratogenic effects in case of pregnancy) or level of cardiovascular risk (24). Recent evidence from a meta-analysis shows that, in hypertensive patients with type 2 diabetes, blockers of the renin–angiotensin system have some greater effectiveness in preventing cardiovascular and renal events than other drug classes (28). Furthermore, it is known that blockers of the renin–angiotensin system appear to be less protective from cardiovascular events in blacks than in whites (29). Finally, the European guidelines (6) indicate other conditions in which some antihypertensive drug classes appear to be preferable, as well as a limited number of conditions to be considered as contraindications or limited indications for any specific class of drugs.

Lengthy discussions on possible advantages of one or another type of monotherapy appear outdated and sterile nowadays, when overwhelming evidence has accumulated that in the large majority of hypertensive patients, blood pressure goals can only be achieved by combination therapy. Because the major limitation to the success of antihypertensive treatment is scarce adherence of patients to lifelong therapy, attention to adverse effects of drugs, either in monotherapy or in combination, is an

| (a) Each class vs. Placebo |       |        |        |        |        |
|----------------------------|-------|--------|--------|--------|--------|
|                            | D     | BB     | CA     | ACEI   | ARB    |
| Stroke                     | Green | Green  | Green  | Green  | Green  |
| CHD                        | Green | Yellow | Yellow | Green  | Yellow |
| HF                         | Green | Green  | Yellow | Green  | Green  |
| Stroke + CHD               | Green | Green  | Green  | Green  | Green  |
| Stroke + CHD + HF          | Green | Green  | Green  | Green  | Green  |
| CV death                   | Green | Yellow | Green  | Yellow | Yellow |
| All-cause death            | Green | Yellow | Green  | Yellow | Yellow |
| Adverse events             | Red   | Red    | Red    | Red    | Yellow |

| (b) Each class vs. all other classes |        |        |        |        |        |
|--------------------------------------|--------|--------|--------|--------|--------|
|                                      | D      | BB     | CA     | ACEI   | ARB    |
| Stroke                               | Yellow | Red    | Green  | Red    | Yellow |
| CHD                                  | Yellow | Yellow | Yellow | Green  | Yellow |
| HF                                   | Green  | Yellow | Red    | Yellow | Yellow |
| Stroke + CHD                         | Yellow | Yellow | Yellow | Yellow | Yellow |
| Stroke + CHD + HF                    | Yellow | Yellow | Yellow | Yellow | Yellow |
| CV death                             | Yellow | Yellow | Yellow | Yellow | Yellow |
| All-cause death                      | Yellow | Yellow | Green  | Yellow | Yellow |
| Adverse events                       | Yellow | Yellow | Yellow | Yellow | Green  |

**Figure 38.6** Comparisons of each of five major classes of antihypertensive agents versus placebo and B, comparisons of each class versus all other classes on seven major outcomes and treatment discontinuations because of adverse events. The effect of each drug class indicated on the top of the columns versus the comparator (a: placebo, b: all other drugs) are indicated as follows: green, better effect; yellow, non-significant difference in effect; red, worse effect. Abbreviations: D, diuretics; BB, beta-blockers; CA, calcium antagonists; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers. CHD, coronary heart disease events; CV, cardiovascular; HF, Heart failure. (From data in Thomopoulos C et al. *J Hellenic Soc Hypertens* 2017; 26: 160–165; Thomopoulos C et al. *J Hypertens* 2015; 33: 195–211; Thomopoulos C et al. *J Hypertens* 2015; 33: 1321–1341.)

important task of practicing physicians, together with an increasing use of two or three drug combinations in single pills. Reducing the number of pills to be taken daily has been shown to improve adherence and increase the rate of blood pressure control.

## REFERENCES

- White PD. *Heart Disease*. 3rd ed. MacMillan, New York; 1944.
- Boerhaave H. *Aphorismes*. Amsterdam; 1709.
- Evans W. Hypertonia or uneventful high blood pressure. *Lancet* 1957; 273: 53–55.
- Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension. 1. Overview, meta-analyses and meta-regression analyses of randomized trials. *J Hypertens* 2014; 32: 2285–2295.
- Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. *Br Med Bull* 1994; 50: 272–298.
- Mancia G, Fagard R, Narkiewicz K et al. Task Force Members 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1281–1357.
- Zanchetti A, Grassi G, Mancia G. When should antihypertensive drug treatment be initiated and to what levels should systolic blood pressure be lowered? A critical reappraisal. *J Hypertens* 2009; 27: 923–934.
- Diao D, Wright JM, Cundiff DK et al. Pharmacotherapy for mild hypertension. *Cochrane Database Syst Rev* 2012; 8: CD006742.
- Sundström J, Arima H, Jackson R et al. Effects of blood pressure reduction in mild hypertension: A systematic review and meta-analysis. *Ann Intern Med* 2015; 162: 184–191.
- Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension. 2. Effects at different baseline and achieved blood pressure levels. Overview and meta-analyses of randomized trials. *J Hypertens* 2014; 32: 2296–2304.
- Lonn EM, Bosch J, López-Jaramillo P et al. HOPE-3 Investigators. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 2016; 374: 2009–2020.
- López-Jaramillo P, Coca A, Sanchez R et al. Hypertension guidelines: Is it time to reappraise blood pressure thresholds and targets? Position of the Latin American Society of Hypertension. *Hypertension* 2016; 68: 257–262.
- Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence. 12. Effects in individuals with high-normal and normal blood pressure: Overview and meta-analyses of randomized trials. *J Hypertens* 2017; 35: 2150–2160.
- Mancia G, De Backer G, Dominiczak A et al. 2007 Guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; 25: 1105–1187.
- Chobanian AV, Bakris GL, Black HR et al. Seventh report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure. *Hypertension* 2003; 42: 1206–1252.
- The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; 373: 2103–2116.
- Zanchetti A, Liu L, Mancia G et al. ESH-CHL-SHOT trial investigators. Continuation of the ESH-CHL-SHOT trial after publication of the SPRINT: Rationale for further study on blood pressure targets of antihypertensive treatment after stroke. *J Hypertens* 2016; 34: 393–396.
- Kjeldsen SE, Lund-Johansen P, Nilsson PM et al. Unattended blood pressure measurements in the Systolic Blood Pressure Intervention Trial: Implications for entry and achieved blood pressure values compared with other trials. *Hypertension* 2016; 67: 808–812.
- Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension. 7. Effects of more versus less intensive blood pressure lowering and different achieved blood pressure levels – updated overview and meta-analyses of randomized trials. *J Hypertens* 2016; 34: 613–622.
- Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension. 8. Outcome reductions versus discontinuations because of adverse drug events – meta-analyses of randomized trials. *J Hypertens* 2016; 34: 1451–1463.
- James PA, Oparil S, Carter BL et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311: 507–520.
- Thomopoulos C, Zanchetti A. Which drugs for hypertension in 2017. *J Hellenic Soc Hypertens* 2017; 26: 160–165.
- Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 4. Effects of various classes of antihypertensive drugs—overview and meta-analyses. *J Hypertens* 2015; 33: 195–211.
- Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 5. Head-to-head comparisons of various classes of antihypertensive drugs—overview and meta-analyses. *J Hypertens* 2015; 33: 1321–1341.
- Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment in hypertension: 9. Discontinuations for adverse events attributed to different classes of antihypertensive drugs: Meta-analyses of randomized trials. *J Hypertens* 2016; 34: 1921–1932.
- Turnbull F, Neal B, Ninomiya T et al. Blood Pressure-Lowering Treatment Trialists' Collaboration. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: Meta-analysis of randomised trials. *Brit Med J* 2008; 336: 1121–1123.
- Turnbull F, Woodward M, Neal B et al. Blood Pressure-Lowering Treatment Trialists' Collaboration. Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials. *Eur Heart J* 2008; 29: 2669–2680.
- Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10—Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. *J Hypertens* 2017; 35: 922–944.
- Ogedegbe G, Shah NR, Phillips C et al. Comparative effectiveness of angiotensin-converting enzyme inhibitor-based treatment on cardiovascular outcomes in hypertensive blacks versus whites. *J Am Coll Cardiol* 2015; 66: 1224–1233.

# THE NEPHROPROTECTIVE EFFECT OF ANTIHYPERTENSIVE TREATMENT

# 39

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## INTRODUCTION

A large amount of clinical and epidemiologic evidence has been accumulated in support of the importance of blood pressure (BP) control in order to reduce chronic kidney disease (CKD) development and progression. It is also generally accepted that suppression of the renin–angiotensin–aldosterone system (RAAS) must be considered in any patient with CKD, in particular if albuminuria is present. Also, the enhancement in global cardiovascular (CV) risk accompanying CKD forces the need to use drugs suppressing the RAAS independently of the influence on renal outcome (1,2).

The term CKD includes the development and evolution of chronic renal failure of many different origins (3). The two most relevant measures used to evaluate the existence of CKD are an estimation of glomerular filtration rate (GFR), usually evaluated through a formula, and the presence of urine albumin (1–3). The need to correctly stratify cardiovascular risk in patients with CKD must be based on the independent predictive capacity of estimated GFR and of albuminuria (4,5). An adequate BP control can improve the evolution of estimated GFR (eGFR) independently of the presence and absence of albuminuria (6). Moreover, in CKD patients, albuminuria has been considered as the key point to recommend a stricter BP goal ( $\leq 130$  mmHg systolic and  $\leq 80$  mmHg diastolic if albumin excretion rate  $\geq 30$  mg/24 h) (1).

Current international guidelines devoted to arterial hypertension recognize albuminuria, elevation of serum creatinine values, and the existence of a low eGFR ( $< 60$  mL/min/1.73 m<sup>2</sup>) as major CV risk factors (7,8) that provide a high added risk on top of the pre-existing one provided by other CV risk factors (9,10). In fact, patients developing end-stage renal disease (ESRD) are a minority in the group of individuals developing the different forms of CKD and could be considered as survivors because cardiovascular disease (CVD) accounts for the death of the great majority of patients with CKD before the development of ESRD. The fact that CKD and CVD are so closely related has increased the interest for investigating the evolution of renal function in trials involving hypertensive as well as heart failure (HF) and post-myocardial infarction (MI) patients. This interest is fully justified by the

demonstration in all of these situations of the predictive capacity of renal function alterations for the development of CV events or death. Since its earlier stages, the presence of CKD must then be considered as a situation of high added CV risk in any hypertensive patient and in any patient presenting with established forms of CVD (11–13).

Reduction of CV events in the CKD population requires the implementation of effective integral therapeutic interventions that simultaneously protect both the kidney and the CV system (14). These interventions have to be implemented at the very initial stages of CKD, and the attainment of strict BP control occupies the first position in the list of things to be done in any patient with an elevated global CV risk, provided BP is found to be elevated (1,2,8,9).

This brief review contains data from recent guidelines, clinical trials and surveys, describing the actual consideration of adequate goal BP in CKD and describing the prevalence of renal and CV endpoints in trials primarily devoted to renal function as well as in those dedicated to arterial hypertension and its CV consequences. The recent data showing the protective cardiorenal capacity of the new oral antidiabetics will also be commented upon.

## THE KIDNEY AND BP

The kidney plays a key role in the control of BP, and impairment of renal function usually leads to the development of arterial hypertension. Thus, high BP can be both a cause and a consequence of CKD (15) and will contribute to an unfavourable renal and CV prognosis. Hypertension-related mechanisms involved in the progression of CKD include the systemic BP load, its direct transmission to the renal microvasculature and glomeruli, and also local factors dependent on the existence of other diseases, like diabetes or primary glomerulonephritis, which by themselves can cause progressive renal damage even in the absence of elevated BP. More recent data have identified several clinical situations related with progression of CKD as subclinical cardiac abnormalities in cardiac structure (16), previous episodes of acute kidney injury (17,18), lower plasma renin activity and higher aldosterone-to-renin ratio



(19), increased fat accumulation in the renal sinus ('fatty kidney') (20) or sympathetic hyperactivity (21). However, elevated BP and the amount of albumin present in urine are the two most relevant factors facilitating the progression of renal failure till ESRD (11). Together, BP and albuminuria are related to the progression of arteriosclerosis and target-organ damage (22,23) and are independent risk factors for cardiovascular and all-cause mortality (24). In recent years, some parameters related to blood pressure have been linked to progression of kidney damage and cardiovascular risk: increased aortic pulse pressure that could be associated with alteration of renal hemodynamics through the pulsatile characteristic of BP (25), the visit-to-visit BP variability as an independent determinant of deterioration of renal function (26), and the influence of out-of-office BP values on progression of renal and cardiovascular disease (27,28,29). Moreover, new methods to estimate renal function could contribute to a better identification of high-risk patients (30–33).

The renoprotection provided by antihypertensive agents depends on their capacity to lower systemic BP and also on their specific effects on renal hemodynamics (34). This effect could positively or negatively influence intraglomerular pressure through the facilitation of the transmission of an uncontrolled systemic BP that, as we know, is present in many patients with CKD even while on treatment and/or through the effect opening or closing the efferent arteriole (34). A meta-analysis of 11 randomized controlled trials assessed the effect of systolic BP (SBP) on the renal outcome in 1860 patients with nondiabetic renal disease (35). The lower risk for progressive renal disease was observed when SBP ranged from 110 to 129 mmHg. Higher levels of SBP were associated with a sudden increase in renal risk, regardless of the drug used. Values of achieved SBP < 110 mmHg were, interestingly, associated with an increased renal risk, consistent with the potential negative renal effects of a drastic reduction in renal perfusion pressure when renal vasculature has suffered the consequences of a maintained elevation of BP and nephrosclerosis has developed (36). Independently of the level of BP attained, antihypertensive regimens that include an angiotensin-converting enzyme inhibitor (ACEi) were more effective than regimens without it for slowing the progression of nondiabetic renal disease. Similar data were found in a secondary analysis of the Irbesartan Diabetic Nephropathy Trial (IDNT); the risk for reaching a renal endpoint in diabetic nephropathy is reduced progressively and continuously at lower levels of the achieved SBP. An optimal renoprotective effect was demonstrated for SBP between 120–130 mmHg, with no further benefits below 120 mmHg (37).

Previous guidelines for kidney disease recommended a BP target <130/80 mmHg for all patients with CKD, irrespective of the level of urine protein (1,7,8), based on observational data in general population and in patients with renal disease (38,39,40). Since the publication of previous guidelines, several manuscripts have emphasized that tight BP control may have adverse effects (41,42). Moreover, several recent trials have not shown a benefit of lower BP targets in patients without proteinuria. In the African American Study of Kidney Disease and Hypertension, there was a benefit associated with the lower BP target among patients with a urine protein/creatinine ratio (PCR) >220 mg/g, but not among those with a lower PCR (43). Similarly, in the Action to Control Cardiovascular Risk in Diabetes trial, no benefit was found with regard to the primary composite

outcome with a systolic BP target <120 mmHg versus a target of <140 mmHg (44). In consequence, it was proposed to extrapolate BP targets currently recommended in the general population (<140/90 mmHg) to those patients with CKD who do not have elevated albuminuria (8,9). Nevertheless, considering that increased urinary albumin excretion is associated with higher cardiovascular and renal risk, guidelines suggested a BP target ≤130/80 mmHg for patients with CKD and increased albuminuria, both with and without diabetes (3,8).

Recently, the publication of the renal data of the Systolic Blood Pressure Intervention Trial (SPRINT), showed that targeting SBP to values <120 mmHg compared with <140 mmHg reduced rates of major CV events and all-cause death without evidence of effect modifications by CKD or deleterious effect on the main kidney outcome (45). However, more intense BP lowering resulted in more frequent episodes of acute kidney injury (AKI), in most cases mild in nature and with a total recovery (46) and in increased risk for incident CKD events, but this was outweighed by cardiovascular and all-cause mortality benefits (47). The new Guidelines of the American College of Cardiology and the American Heart Association (48) consider that attaining BP values below 130/80 mmHg is an adequate goal for patients with CKD.

## RECENT TRIALS FOCUSING ON RENAL OUTCOMES

RAAS blockade is strongly recommended by most recent guidelines as the initial regimen of choice for renoprotection based on the results of several clinical trials and meta-analyses that have, with hardly any exception, revealed larger reductions in proteinuria as well as a diminished velocity of progression to the development of renal endpoints with RAAS blockade as compared with other antihypertensive regimens in both diabetic and nondiabetic nephropathies (49). As an example, the previously mentioned meta-analysis conducted by Jafar et al. (35) suggests that ACE inhibition was associated with overall relative risk reductions of 30–40% for doubling of serum creatinine and/or ESRD in nondiabetic nephropathy, with the greater benefits being seen in patients with heavier proteinuria. Such data indicate that the greater renoprotection that is observed with RAAS blockade is mediated by BP-independent mechanisms.

Similar positive results with suppression of the RAAS, beyond BP control, were seen in the patients included in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and IDNT studies in patients with overt diabetic nephropathy, and two angiotensin receptor blockers (ARBs), losartan and irbesartan, were compared to placebo and placebo or amlodipine, respectively (50,51). The advantage of RAAS suppression was also demonstrated for the prevention of the development of overt diabetic nephropathy in the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA) study (52). This study showed that treatment with the ARB irbesartan was more effective than placebo in preventing the development of macroalbuminuria and also in favouring regression to normoalbuminuria in microalbuminuric patients with type 2 diabetes, despite a similar BP control.



The concept of nephroprotection during dual blockade of RAAS with combination therapy of an ACEi and an ARB or with either of these two and aliskiren have been discarded because of the absence of positive results in different trials (8,48).

In recent years, aldosterone is regarded as a mediator of progressive renal damage (53). It is therefore relevant that aldosterone antagonists reduce proteinuria in patients with chronic kidney disease, even if they are already on a RAAS blocker (54,55). In a meta-analysis, the addition of an aldosterone antagonist to an ACEi or an ARB, decreased proteinuria by an estimate of 30–40% (55). A limiting factor for the wide use of aldosterone antagonists is linked with the risk of inducing hyperkalaemia, which becomes a prominent concern as renal function deteriorates (54,55). The recent appearance of new potassium binders could facilitate the maintenance of RAAS blockade including an ACEi or an ARB plus an aldosterone blocker in patients with stage 3–4 or more advanced CKD (56) because of their capacity to control increases in serum potassium that impede adequate RAAS blockade.

These data indicate that a better degree of suppression of the RAAS is obtained with the combination therapy but leave open the possibility that doses higher than those normally used for each component could be equally positive as the combination at lower doses (57). In this sense, recently published data have shown that up-titration of the dose of an ARB improves its capacity to diminish albuminuria (58,59). Up-titration of the dose of an ARB is important because the only head-to-head comparison between an ACEi and an ARB, performed in the Diabetics Exposed to Telmisartan and enalapril (DETAIL) study (60) for the long-term renal outcome in mostly microalbuminuric type 2 diabetics, showed that telmisartan offered comparable nephroprotection to enalapril. These new options, together with a multifactorial approach, should be considered because the traditional chronic RAAS suppression does not seem to consistently maintain its protective capacity on the development and evolution of albuminuria both in diabetic and nondiabetic hypertensive patients (61).

## TRIALS NOT FOCUSED ON RENAL OUTCOMES

As previously noted, the capacity of renal function abnormalities to predict CV events and death in patients with arterial hypertension and established CVD raised the interest to investigate, in post hoc analyses, the evolution of renal function, determined exclusively as eGFR or creatinine clearance in different trials including hypertensive patients, patients with HF and also post-MI patients. Data from these trials must be received with some caution, because trials devoted to CVD frequently exclude patients with renal disease and do not provide adequate information on the renal function of enrollees (62). In fact, a meta-analysis including both trials primarily devoted to renal disease and primarily devoted to CVD has come to question the value of suppression of the RAAS beyond BP control in order to protect renal function (63). The use of adequate dosages of an ACEi or an ARB and for the adequate length of follow-up is essential in order to conclude on beneficial or detrimental actions related to their effects. An accurate analysis of the studies included in the

meta-analysis shows that in those not primarily devoted to renal function this was not the case, in particular when Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), which mostly drove the result of the meta-analysis due to the high number of patients included, is considered (64). With respect to the time of follow-up, it is well recognized that, only in the presence of albuminuria, short follow-up periods of 2–5 years are adequate to show potential differences in renal protection (65). Preliminary data with longer follow-up periods indicate that suppression of the RAAS is required for a better renal protection (66).

Even so, data from trials devoted to hypertension and to renal disease have come to clarify the positive role of calcium antagonists in renal protection when used either alone or in combination with drugs suppressing the RAAS (67). More recently, the Delapril and Manidipine for Nephroprotection in Diabetes (DEMAND) trial failed to slow GFR decline after 3.8 years of median follow-up, but safely ameliorated CVD, retinopathy and neuropathy in hypertensive type 2 diabetic patients receiving combined manidipine and delapril therapy (68). It has also been shown that patients with hypertension or established CVD and CKD seem to be particularly good responders to the suppression of the RAAS (69,70) and to the administration of a statin (71) and aspirin (72). The Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure-Lowering Arm (ASCOT-BLPA) showed a 15% reduction of development of renal impairment in high-risk hypertensive patients receiving a combination of amlodipine and perindopril (73). Moreover, the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial showed that patients with hypertension, chronic kidney disease, and minimal or no albuminuria who achieved blood pressure of 130/80 mmHg with an initial combination of benazepril plus amlodipine have lower rates of cardiovascular events and slower progression of chronic kidney disease than do patients treated with a combination of benazepril plus hydrochlorothiazide (74).

## EVIDENCE WITH OTHER THERAPIES AND RENAL OUTCOMES

Individuals with CKD usually present with multiple other risk factors for CVD, and the risks attributable to CKD or to the presence of the other factors are totally independent from each other (75). Drugs other than antihypertensives can also present positive effects on renal function as well as on BP control. This is the case for the effects of statins (76,77), fibrates (78,79), thiazolidinediones (80) or antiplatelet therapy (81,82). Further studies are needed to clarify the potential benefits of other therapies such as allopurinol (83) or vitamin D supplementation (84).

## THE ROLE OF NEW ANTIDIABETIC DRUGS IN THE CONTROL OF BP

Recently, the demonstration that new oral antidiabetic drugs significantly improve the CV and renal outcome of type 2 diabetic patients has introduced conceptually

a radical change in the treatment of these patients. Studies like Empagliflozin Cardiovascular Outcomes and Mortality in Type 2 Diabetes (EMPA-REG [85,86]), The Canagliflozin Cardiovascular Assessment Study (CANVAS [87]), Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER [88,89]) and the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6 [90]) trials have shown very positive results for major adverse cardiovascular events (MACE) and progression of renal disease which are accompanied, among other positive mechanisms, by a significant decrease in body weight and BP. Both mechanisms participate in the improvement in MACE, albeit the descent is rather modest (around 5 mmHg in SBP and less than 5% in body mass index) [39].

In summary, strict BP control, adequate suppression of the RAAS, and an integral protection of the increased global CV risk are required in every patient presenting with any stage of CKD.

## REFERENCES

- Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* 2004; 43: S1–290.
- Wheeler DC, Becker GJ. Summary of KDIGO guideline. What do we really know about management of blood pressure in patients with chronic kidney disease? *Kidney Int* 2013 March; 83(3): 377–383.
- Ruilope LM, Bakris GL. Renal function and target organ damage in hypertension. *Eur Heart J* 2011; 32: 1599–1604.
- Whaley-Connell A, Shlipak MG, Inker LA et al. Awareness of kidney disease and relationship to end-stage renal disease and mortality. *Am J Med* 2012; 125: 661–669.
- Lien YH. Mystery of chronic kidney disease awareness. *Am J Med* 2012; 125: 625–627.
- Hu B, Gadegbeku C, Lipkowitz MS et al. Kidney function can improve in patients with hypertensive CKD. *J Am Soc Nephrol* 2012; 23: 706–713.
- Chobanian A, Bakris GL, Black HR et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 Report. *JAMA* 2003; 289: 2560–2572.
- Mancia G, De Backer G, Dominiczak A et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; 25: 1105–1187.
- Van der Velde M, Matsushita K, Corsh J et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int* 2011; 79: 1341–1352.
- Gansevoort RT, Matsushita K, van der Velde M et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int* 2011; 80: 93–104.
- Segura J, Garcia-Donaire JA, Praga M, Ruilope LM. Chronic kidney disease as a situation of high-added risk in hypertensive patients. *J Am Soc Nephrol* 2006; 17(Suppl 2): S136–S140.
- Fox CS, Matsushita K, Woodward M et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: A meta-analysis. *Lancet* 2012; 380: 1662–1673.
- Tonelli M, Muntner P, Lloyd A et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: A population-level cohort study. *Lancet* 2012; 380: 807–814.
- Ruiz-Hurtado G, Ruilope LM. Does cardiovascular protection translate into renal protection? *Nat Rev Cardiol* 2014; 11: 742–746.
- Ruilope LM, Lahera V, Rodicio JL, Romero JC. Are renal hemodynamics a key factor in the development and maintenance of arterial hypertension in humans? *Hypertension* 1994; 23: 3–9.
- Park M, Shlipak MG, Katz R et al. Subclinical cardiac abnormalities and kidney function decline: The multi-ethnic study of atherosclerosis. *Clin J Am Soc Nephrol* 2012; 7: 1137–1144.
- Bellomo R, Kellum JA, Ronco C. Acute kidney injury. *Lancet* 2012; 380: 756–766.
- Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: A systematic review and meta-analysis. *Kidney Int* 2012; 81: 442–448.
- Terata S, Kikuya M, Satoh M et al. Plasma renin activity and the aldosterone-to-renin ratio are associated with the development of chronic kidney disease: The Ohasama Study. *J Hypertens* 2012; 30: 1632–1638.
- Foster MC, Hwang SJ, Porter SA et al. Fatty kidney, hypertension and chronic kidney disease. The Framingham Heart Study. *Hypertension* 2011; 58: 784–790.
- Vink EE, de Jager RL, Blankestijn PJ. Sympathetic hyperactivity in chronic kidney disease: pathophysiology and (new) treatment options. *Curr Hypertens Rep* 2013; 15(2): 95–101.
- Turner ST, Rule AD, Schwartz GL et al. Risk factor profile for chronic kidney disease is similar to risk factor profile for small artery disease. *J Hypertens* 2011; 29: 1796–1801.
- Shah AM, Lam CSP, Cheng S et al. The relationship between renal impairment and left ventricular structure, functions and ventricular-arterial interaction in hypertension. *J Hypertens* 2011; 29: 1829–1836.
- Oh SW, Baek SH, Kim YC et al. Mild decrease in estimated glomerular filtration rate and proteinuria are associated with all-cause and cardiovascular mortality in the general population. *Nephrol Dial Transplant* 2012; 27: 2284–2290.
- Hashimoto J, Ito S. Central pulse pressure and aortic stiffness determine renal hemodynamics. Pathophysiological implication for microalbuminuria in hypertension. *Hypertension* 2011; 58: 839–846.
- Yokota K, Fukuda M, Matsui Y et al. Impact of visit-to-visit variability of blood pressure on deterioration of renal function in patients with non-diabetic chronic kidney disease. *Hypertens Res* 2013; 36: 151–157.
- Okada T, Matsumoto H, Nagaoka Y et al. Association of home blood pressure variability with progression of chronic kidney disease. *Blood Press Monit* 2012; 17: 1–7.
- Palatini P. Ambulatory blood pressure and cardiovascular risk in chronic kidney disease. *Curr Hypertens Rep* 2008; 10: 119–126.
- Kario K. Proposal of RAS-diuretic vs RAS-calcium antagonists strategies in high-risk hypertension: Insight from the 24-hour ambulatory blood pressure profile and central pressure. *J Am Soc Nephrol* 2010; 4: 215–218.
- Earley A, Mikulin D, Lamb EJ et al. Estimating Equations for glomerular filtration rate in the era of creatinine standardization. A systematic review. *Ann Intern Med* 2012; 156: 785–795.
- Matsushita K, Mahmoodi BK, Woodward M et al. Chronic Kidney Disease Prognosis Consortium. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA* 2012; 307: 1941–1951.
- Inker LA, Schmid CH, Tighiouart H et al. For the CKD-EPI investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012; 367: 20–29.
- Peralta CA, Shlipak MG, Judd S et al. Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. *JAMA* 2011; 305: 1545–1552.
- Taal MW. Slowing the progression of adult chronic kidney disease. Therapeutic advances. *Drugs* 2004; 64: 2273–2289.
- Jafar TH, Stark PC, Schmid CH et al. AIPRD Study Group. Progression of chronic kidney disease: The role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: A patient-level meta-analysis. *Ann Intern Med* 2003; 139: 244–252.
- Toto RD. Renal insufficiency due to angiotensin-converting enzyme inhibitors. *Miner Electrolyte Metab* 1994; 20: 193–200.
- Pohl MA, Blumenthal S, Cordonnier DJ et al. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the Irbesartan Diabetic Nephropathy Trial: Clinical implications and limitations. *J Am Soc Nephrol* 2005; 16: 3027–3037.
- Go AS, Chertow GM, Fan D et al. Chronic kidney disease and the risks of death, cardiovascular events and hospitalization. *N Engl J Med* 2004; 31: 1296–1305.
- Sarnak MJ, Levey AS, Schoolwerth AC et al. Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on kidney

- in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. *Circulation* 2003; 108: 2154–2169.
40. Peterson JC, Adler S, Burkart JM et al. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Ann Intern Med* 1995; 123: 754–762.
  41. Weiner DE, Tighiouart H, Levey AS et al. Lowest systolic blood pressure is associated with stroke in stages 3 to 4 chronic kidney disease. *J Am Soc Nephrol* 2007; 18: 960–966.
  42. Lewis JB. Blood pressure control in chronic kidney disease: Is less really more? *J Am Soc Nephrol* 2010; 21: 1086–1092.
  43. Appel LJ, Wright JT Jr, Greene T et al. Intensive blood pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010; 363: 918–929.
  44. Cushman WC, Evans GW, Byington RP et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; 362: 1575–1585.
  45. Cheung AK, Rahaman M, Reboussin DM et al. Effects of intensive BP control in CKD. *J Am Soc Nephrol* 2017; 28: 2812–2823.
  46. Rocco MV, Sink KM, Lovato LC et al. Effects of intensive blood pressure treatment on acute kidney injury events in the Systolic Blood Pressure Intervention Trial (SPRINT). *Am J Kidney Dis* 2018; 71(3): 352–361.
  47. Beddhu S, Rocco BS, Toto R et al. Effects of intensive systolic blood pressure control on kidney and cardiovascular outcomes in persons without kidney disease: A secondary analysis of a randomized trial. *Ann Intern Med* 2017; 167(6): 375–383.
  48. Whelton PK, Carey RM, Aronow WS et al. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. [Published on line November 13, 2017.] *Hypertension* 2018; 72(3): e33.
  49. Becker GJ, Wheeler DC, De Zeeuw D et al. Kidney disease: Improving global outcomes (KDIGO) blood pressure working group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int* 2012; 2(Suppl): 337–414.
  50. Brenner BM, Cooper ME, de Zeeuw D et al. RENAAL Study Investigators. Effect of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; 345: 861–869.
  51. Lewis EJ, Hunsicker LG, Clarke WR et al. Collaborative Study Group. Renoprotective effect of the angiotensin receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; 345: 851–860.
  52. Parving HH, Lehnert H, Brochner-Mortensen J et al. Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001; 345: 870–878.
  53. Epstein M. Aldosterone and the hypertensive kidney: Its emerging role as a mediator of progressive renal dysfunction: a paradigm shift. *J Hypertens* 2001; 19: 829–842.
  54. Navaneethan SD, Nigwekar SU, Sehgal AR et al. Aldosterone antagonists for preventing the progression of chronic kidney disease: A systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2009; 4: 542–551.
  55. Bombardier AS, Kshirsagar AV, Amamoo MA et al. Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: A systematic review. *Am J Kidney Dis* 2008; 51: 199–211.
  56. Zannad F, Rossignol P, Stough WG et al. New approaches to hyperkalemia in patients with indications for renin angiotensin aldosterone inhibitors: Considerations for trial design and regulatory approval. *Int J Cardiol* 2016; 216: 46–51.
  57. Segura J, Christiansen H, Campo C, Ruilope LM. How to titrate ACE inhibitors and angiotensin receptor blockers in renal patients: According to blood pressure or proteinuria? *Curr Hypertens Rep* 2003; 5: 426–429.
  58. Rossing K, Schjoedt KJ, Jensen BR et al. Enhanced renoprotective effects of ultrahigh doses of irbesartan in patients with type 2 diabetes and microalbuminuria. *Kidney Int* 2005; 68: 1190–1198.
  59. Schmieder RE, Klingbeil AU, Fleischmann EH et al. Additional antiproteinuric effect of ultrahigh dose candesartan: A double-blind, randomized, prospective study. *J Am Soc Nephrol* 2005; 16: 3038–3045.
  60. Barnett AH, Bain SC, Bouter P et al. Diabetics Exposed to Telmisartan and Enalapril Study Group. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004; 351: 1952–1961.
  61. Cerezo C, Ruilope LM, Segura J et al. Microalbuminuria breakthrough under chronic renin-angiotensin-aldosterone system suppression. *J Hypertens* 2012; 30: 204–209.
  62. Coca SG, Krumholz HM, Garg AX, Parikh CR. Underrepresentation of renal disease in randomized controlled trials of cardiovascular disease. *JAMA* 2006; 296: 1377–1384.
  63. Casas JP, Chua W, Loukogeorgakis S et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: Systematic review and meta-analysis. *Lancet* 2005; 366: 2026–2033.
  64. Hollenberg NK, Epstein M. Renin angiotensin system blockade and nephropathy: Why is it being called into question, and should it be? *Clin J Am Soc Nephrol* 2006; 1: 1046–1048.
  65. Halbesma N, Kuiken D, Brantsma AH et al. Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. *J Am Soc Nephrol* 2006; 17: 2582–2590.
  66. Segura J, Campo C, Rodicio JL, Ruilope LM. ACE inhibitors and appearance of renal events in hypertensive nephrosclerosis. *Hypertension* 2001; 38(3 Pt 2): 645–649.
  67. Segura J, Garcia-Donaire JA, Ruilope LM. Calcium channel blockers and renal protection: Insights from the latest clinical trials. *J Am Soc Nephrol* 2005; 16: S64–S66.
  68. Ruggenenti P, Lauria G, Iliev IP et al. Effects of manidipine and delapril in hypertensive patients with type 2 diabetes mellitus. *Hypertension* 2011; 58: 776–783.
  69. Segura J, Campo C, Gil P et al. Development of chronic kidney disease and cardiovascular prognosis in essential hypertensive patients. *J Am Soc Nephrol* 2004; 15: 1616–1622.
  70. Mann JF, Gerstein HC, Pogue J et al. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. *Ann Intern Med* 2001; 134: 629–636.
  71. Tonelli M, Keech A, Shepherd J et al. Effect of pravastatin in people with diabetes and chronic kidney disease. *J Am Soc Nephrol* 2005; 16: 3748–3754.
  72. Zanchetti A, Hansson L, Leonetti G et al. Low-dose aspirin does not interfere with the blood pressure lowering effects of antihypertensive therapy. *J Hypertens* 2002; 20: 1015–1022.
  73. Dahlöf B, Sever PS, Poulter NR et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): A multicentre randomised controlled trial. *Lancet* 2005; 366: 895–906.
  74. Bakris GL, Sarafidis PA, Weir MR et al. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): A prespecified secondary analysis of a randomised controlled trial. *Lancet* 2010; 375: 1173–1181.
  75. Weiner DE, Tabatabai S, Tighiouart H et al. Cardiovascular outcomes and all-cause mortality: Exploring the interaction between CKD and cardiovascular disease. *Am J Kidney Dis* 2006; 48: 392–401.
  76. Douglas K, O'Malley PG, Jackson JL. Meta-analysis: The effect of statins on albuminuria. *Ann Intern Med* 2006; 145: 117–124.
  77. Ku E, Campese V. Is lipid management effective for all stages of CKD? *Blood Purif* 2013; 35: 26–30.
  78. Jun M, Zhu B, Tonelli M et al. Effects of fibrates in kidney disease. A systematic review and meta-analysis. *J Am Coll Cardiol* 2012; 60: 2061–2071.
  79. McCollough PA, Di Loreto MJ. Fibrates and cardiorenal outcomes. *J Am Coll Cardiol* 2012; 60: 2072–2073.
  80. Sarafidis PA, Bakris GL. Protection of the kidney by thiazolidinediones: An assessment from bench to bedside. *Kidney Int* 2006; 70: 1223–1233.
  81. Jardine MJ, Ninomiya T, Perkovic V et al. Aspirin is beneficial in hypertensive patients with chronic kidney disease: A post-hoc subgroup analysis of a randomized controlled trial. *J Am Coll Cardiol* 2010; 56: 956–966.
  82. Palmer SC, Di Micco L, Razavian M et al. Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease. A systematic review and meta-analysis. *Ann Intern Med* 2012; 156: 445–459.
  83. Kabul S, Shepler B. A review investigating the effect of allopurinol on the progression of kidney disease in hyperuricemic patients with chronic kidney disease. *Clin Ther* 2012; 34: 2293–2296.
  84. Anker SD, von Haehling S. Vitamin D in chronic kidney disease. More questions than answers. *JAMA* 2012; 307: 722–723.

85. Zinman B, Wanner C, Lachin JM et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373: 2117–2128.
86. Wanner C, Inzucchi SE, Zinman B. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016; 375: 1801–1802.
87. Neal B, Perkovic V, Mahaffey KW et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377: 644–657.
88. Marso SP, Daniels GH, Brown-Frandsen K et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; 375: 311–322.
89. Mann JFE, Ørsted DD, Brown-Frandsen K et al. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 2017; 377: 839–848.
90. Marso SP, Bain SC, Consoli A et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; 375: 1834–1844.



# ANTIHYPERTENSIVE DRUG CLASSES

# 40

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## INTRODUCTION

In this chapter, we review basic pharmacological characteristics of antihypertensive drug classes and selected drugs. We primarily focus, in addition to available reports and textbook material (1–3), on the major drug classes that are suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in combination therapy as recommended in European guidelines (4). In addition, drug classes preferred in specific conditions as well as other drugs particularly used in patients with treatment-resistant hypertension are briefly summarized. Finally, a synopsis of novel drugs for the treatment of hypertension and associated diseases is presented.

## DRUGS FOR INITIATION AND MAINTENANCE OF ANTIHYPERTENSIVE TREATMENT

### INHIBITORS OF RENIN-ANGIOTENSIN SYSTEM

Three classes of available drugs act on the renin-angiotensin system (RAS): angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), and aliskiren, an orally active renin antagonist. The latter is, however, not recommended for initiation and maintenance of antihypertensive ('first-line') treatment (4).

#### ACE INHIBITORS

##### MECHANISM OF ACTION

The core of the RAS pathway involves the conversion of angiotensinogen to angiotensin I (Ang I) by renin followed by its conversion to angiotensin II (Ang II) by ACE. Ang II acts via activation of angiotensin II receptor type 1 to induce arterial vasoconstriction, aldosterone synthesis and secretion, thus increasing sodium and water reabsorption and increasing blood pressure (BP) (3). ACE is also capable of degrading bradykinin (a potent vasodepressor

peptide) which contributes to the increase in BP. ACE inhibitors inhibit competitively the activity of ACE resulting in downstream reduction of Ang II in blood and tissues as well as reduction of aldosterone secretion and stimulation of kallikrein-kinin system (1).

##### CLASSIFICATION

ACE inhibitors share the same basic structure, but they can be differentiated according to their functional group into those containing a sulfhydryl (captopril), a carboxyl (most of them) or a phosphoryl group (fosinopril). These functional groups act as ligands to the zinc atom of the ACE molecule and are partly responsible for differences in their pharmacokinetic as well as safety profiles (5). According to their mode of metabolism, three subgroups of ACE inhibitors can be identified:

- Active compounds that are metabolized to form active metabolites (e.g. captopril)
- Prodrugs that require hepatic bioactivation (e.g. enalapril)
- Active compounds that are excreted unchanged (e.g. lisinopril)

##### PHARMACOKINETICS AND DOSING

Gastrointestinal absorption is highly variable among ACE inhibitors (25–75%) and food either has no effect or reduces the rate, but not the extent, of absorption. The peak plasma drug concentrations are reached 1–4 h after ingestion. All ACE inhibitors bind to tissue and plasma proteins (1). Most ACE inhibitors and their metabolites are excreted mainly by the kidneys, and to minor extent by the liver (Table 40.1). Consequently, increased plasma concentrations and prolongation of half-life of ACE inhibitors is observed particularly in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m<sup>2</sup>) and thus dose adjustments should be considered. For maintenance dosing, once- or twice-daily dosing is usually sufficient for BP control except for captopril (requiring at least 2–3 doses per day), which has the shortest duration of action. ACE inhibitors may increase plasma levels of lithium, especially in elderly patients (3).



**Table 40.1** Pharmacokinetic characteristics and dosage of selected ACE inhibitors

| Drug                      | Half-life (h) | Daily frequency of administration | Usual dosing range (mg/day) | Renal elimination (%) <sup>a</sup> |
|---------------------------|---------------|-----------------------------------|-----------------------------|------------------------------------|
| Benazepril <sup>b</sup>   | 11            | 1–2                               | 10–40                       | 70                                 |
| Captopril                 | 2             | 2–3                               | 12.5–150                    | 55                                 |
| Enalapril <sup>b</sup>    | 11            | 1–2                               | 5–40                        | 80                                 |
| Fosinopril <sup>b</sup>   | 12            | 1                                 | 10–40                       | 50                                 |
| Lisinopril                | 12            | 1                                 | 10–40                       | 80                                 |
| Perindopril <sup>b</sup>  | >24           | 1                                 | 4–16                        | 73                                 |
| Quinapril <sup>b</sup>    | 2–4           | 1–2                               | 10–80                       | 80                                 |
| Ramipril <sup>b</sup>     | 13–17         | 1–2                               | 2.5–10                      | 70                                 |
| Trandolapril <sup>b</sup> | 16–24         | 1                                 | 1–4                         | 56                                 |

<sup>a</sup> Renal impairment (6), particularly if severe with an eGFR is <30 mL/min/1.73 m<sup>2</sup> may require cautious use and dose adjustment of drugs. This may generally apply to drugs for which the renal elimination rate is at least 50%.

<sup>b</sup> Prodrug.

## ADVERSE EFFECTS

ACE inhibitors are well tolerated in most patients. There are no significant differences between different ACE inhibitors in terms adverse effect profiles (2).

**Dry cough:** Cough is not dose-dependent and may develop from 1 week to a few months of treatment. It is a class effect due to increased levels of bradykinin and/or substance P in the lungs and may require treatment discontinuation or impair adherence to drug treatment.

**Hyperkalaemia:** May occur due to the decrease in aldosterone secretion. It is more likely with renal insufficiency, congestive heart failure and in the elderly. Concomitant administration of potassium-sparing diuretics or nonsteroidal anti-inflammatory drugs can aggravate hyperkalaemia.

**Renal impairment:** ACE inhibitors can impair renal function due to their vasodilatory effect on the glomerular efferent arteriole, thereby reducing glomerular filtration pressure and hence GFR. On the other hand, to unload the glomerulus from increased pressure is one of the most important mechanisms by which all RAS inhibitors reduce albuminuria/proteinuria and protect from progression of chronic kidney disease (CKD). The degree of impairment is greater when renal perfusion pressure is low, and filtration pressure critically depends on Ang II such as in patients with volume depletion, hyponatremia and bilateral renal artery stenosis and advanced CKD. Elderly patients with congestive heart failure are also prone to this. Recovery of renal function frequently occurs after drug discontinuation.

**Angioedema:** A rare but potentially fatal adverse effect, caused by accumulation of bradykinin. Symptoms range from mild gastrointestinal disturbances to significant diarrhoea or severe dyspnoea (due to laryngeal oedema), and death. It occurs more frequently within the first month of therapy and disappears after discontinuation of the ACE inhibitor.

**Teratogenic effects:** ACE inhibitors are contraindicated during the second and third trimesters of pregnancy because of the risk of fetal abnormalities or death. Exposure to ACE inhibitors during the first trimester increases the teratogenic risk as well. Thus ACE inhibitors should be avoided in women with childbearing potential without reliable

contraception (Table 40.4) and discontinued if pregnancy is suspected or diagnosed.

## ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

### MECHANISM OF ACTION

In contrast to ACE inhibitors, ARBs reduce the effects of Ang II on BP by blocking AT<sub>1</sub> receptors. In addition, activation of unblocked AT<sub>2</sub> receptors by Ang II might contribute to BP-lowering effects of ACE inhibitors and ancillary beneficial effects of ARBs (7). Overall, ARBs reduce blood pressure as effectively as ACE inhibitors (1).

### CLASSIFICATION

ARBs have a similar common molecular structure, with the exception of eprosartan, and exhibit pharmacological differences in lipid solubility, binding affinity to AT<sub>1</sub> receptor and pharmacokinetic profile. Three ARBs (candesartan cilexetil, olmesartan medoxomil, azilsartan medoxomil) are prodrugs and require activation in the gastrointestinal tract and liver to their active forms (3).

### PHARMACOKINETICS AND DOSING

The bioavailability of ARBs ranges from 13% for eprosartan to about 60% for irbesartan and telmisartan. Losartan undergoes first-pass metabolism in the liver via the cytochrome P450 (CYP) system to form EXP3174, which is more potent than parenteral losartan. Protein binding for all ARBs is high, but they vary widely in their volume of distribution from 10 L for candesartan to 500 L for telmisartan. ARBs exhibit considerably different plasma half-lives, although this does not necessarily correlate with the duration of their BP-lowering effect (Table 40.2). Contrary to ACE inhibitors, the mode of elimination for ARBs is predominantly hepatic; therefore, no dosage adjustment based on pharmacokinetic rationales is required in patients with impaired renal function (7). Losartan has a potential for drug interactions due to its metabolism by CYP2C9, which is important to generate EXP-3174. Inhibition of

**Table 40.2** Pharmacokinetic characteristics and dosage of selected angiotensin receptor blockers (ARBs)

| Drug        | Half-life (h) | Daily frequency of administration | Usual dosing range (mg) | Renal elimination <sup>a</sup> |
|-------------|---------------|-----------------------------------|-------------------------|--------------------------------|
| Azilsartan  | 12            | 1                                 | 40–80                   | 95%                            |
| Candesartan | 9             | 1                                 | 8–32                    | 60%                            |
| Eprosartan  | 5–9           | 1–2                               | 600–800                 | 10%                            |
| Irbesartan  | 11–15         | 1                                 | 150–300                 | –                              |
| Losartan    | 2             | 1–2                               | 50–100                  | 5%                             |
| Olmesartan  | 12–14         | 1                                 | 20–40                   | 40%                            |
| Telmisartan | 24            | 1                                 | 20–80                   | –                              |
| Valsartan   | 6             | 1                                 | 80–320                  | 30%                            |

<sup>a</sup> See Table 40.1; –, indicates almost no renal elimination.

this enzyme with concomitant drugs (e.g. azole antimycotics) will increase losartan levels but decrease EXP-3174, while inducers like rifampin will increase the clearance of both losartan and EXP-3174. Telmisartan may cause variable increases in serum digoxin levels, mandating monitoring digoxin levels during concomitant therapy (2).

#### ADVERSE EFFECTS

ARBs are very well tolerated and associate with treatment discontinuation rates due to adverse events that are similar to placebo treatment and lower than those observed with all other antihypertensive drugs (4,7). Hence cough and angioedema are not associated with ARB treatment. All other aspects for adverse effects mentioned above for ACE inhibitors apply also to ARBs.

### CALCIUM CHANNEL BLOCKERS

#### MECHANISM OF ACTION

Calcium channel blockers (CCBs) inhibit the influx of extracellular calcium through L-type channels located on the vascular smooth muscle, cardiac myocytes, and cardiac nodal tissue (sinoatrial and atrioventricular nodes) (1). The inhibition of inward calcium flux causes relaxation of vascular smooth muscle cells and results in vasodilation and lowering of BP. In cardiac muscle, contractility is reduced and conduction velocities in cardiac nodal tissue are slowed (2).

#### CLASSIFICATION OF CCBs

There are two main groups of CCBs, the dihydropyridine-type (DHP) CCB (e.g. nifedipine and amlodipine) and the non-dihydropyridine type (non-DHP), which can be further subdivided into benzothiazepines, such as diltiazem, and phenylalkylamines, such as verapamil (Table 40.3). The CCBs are a chemically diverse group with a common mechanism of action, however they differ in their relative selectivity toward cardiac versus vascular L-type calcium channels (8). Whereas DHPs are more vasoselective than non-DHP, non-DHPs have a more negative chronotropic and inotropic effect than DHPs. Being potent arterial vasodilators, particularly rapid- and short-acting DHP CCBs exhibit the potential of baroreflex-mediated activation of

the sympathetic nervous system resulting in tachycardia (2). Therefore, formulations and compounds with delayed onset and longer duration of action have replaced the rapid- and short-acting oral medications. DHPs were classified into first, second, third or fourth generation DHP CCBs based on their sequence of development and duration of action. The first generation comprises the original formulations of nifedipine and nicardipine (8). Their clinical use was significantly limited by rapid onset and short half-life, which predispose to adverse effects. Subsequent generations of DHP CCBs comprise either first-generation drugs with longer-acting formulations or CCBs with novel chemical structures and increasingly longer half-lives.

#### PHARMACOKINETICS AND DOSING

CCBs have a high first-pass effect, high plasma protein binding and extensive metabolism (3). During repeated oral administration, bioavailability and half-life may increase because of saturation of hepatic metabolism. Both metabolism and pre-systemic clearance of all CCBs are mediated by CYP3A4. In addition, all CCBs are also a substrate of P-glycoprotein (P-gp), an efflux transporter. Importantly, however, only verapamil and diltiazem exhibit a significant inhibiting effect on both CYP3A4 and P-gp. This results in their potential to cause adverse drug–drug interactions when verapamil and diltiazem are administered together with drugs that are substrates of CYP3A4 and/or P-gp. In this situation, plasma concentrations of the other substrates will rise, thereby increasing their toxicity (1). For example, verapamil and diltiazem increase the risk of myopathy of some statins, nephrotoxicity of cyclosporine and tacrolimus, digoxin toxicity, and increased plasma concentrations of novel oral anticoagulants (NOACs), thereby increasing the risk for bleeding events. On the other hand, the use of CYP3A4 and/or P-gp inhibitors can increase the plasma concentrations of all CCBs and thus impair their tolerability (1).

#### ADVERSE EFFECTS

The CCBs are generally well-tolerated drugs. Their adverse effects derive from their pharmacologic properties (2). Gastrointestinal adverse effects include gastroesophageal reflux, slowed gastrointestinal transit and constipation

**Table 40.3** Pharmacokinetic characteristics and dosage of selected calcium channel blockers

| Drug                            | Half-life (h) | Daily frequency of administration | Usual dosing range (mg/day) | Renal elimination <sup>a</sup> |
|---------------------------------|---------------|-----------------------------------|-----------------------------|--------------------------------|
| <b>CCB—Dihydropyridines</b>     |               |                                   |                             |                                |
| Amlodipine                      | 30–50         | 1                                 | 2.5–10                      | 15%                            |
| Felodipine                      | 11–16         | 1                                 | 5–10                        | –                              |
| Isradipine                      | 8–12          | 2                                 | 5–10                        | –                              |
| Nicardipine SR                  | 8–12          | 2                                 | 60–120                      | <1%                            |
| Nifedipine LA                   | 2             | 1                                 | 30–120                      | –                              |
| Nisoldipine SR                  | 7–12          | 1                                 | 30–90                       | –                              |
| Lercanidipine                   | 2–5           | 1                                 | 10–20                       | –                              |
| Lacidipine                      | 13–18         | 1                                 | 2–6                         | –                              |
| <b>CCB—Non-dihydropyridines</b> |               |                                   |                             |                                |
| Diltiazem SR                    | 2.5           | 2                                 | 180–360                     | <10%                           |
| Diltiazem ER                    | 5–10          | 1                                 | 120–480                     | <10%                           |
| Verapamil IR                    | 4.5–12        | 3                                 | 40–80                       | 4%                             |
| Verapamil SR                    | 4.5–12        | 1–2                               | 120–480                     | 4%                             |

Abbreviations: SR, sustained release; LA, long acting; ER, extended release; IR, immediate release.

<sup>a</sup> See Table 40.1; –, indicates almost no renal elimination.

(particularly with verapamil). Gingival hypertrophy can occur with all CCBs. Flushing, headache, tachycardia and peripheral oedema are more common with DHP. Peripheral oedema is not due to fluid retention but occurs because of the imbalance between upstream arteriolar vasodilatation and downstream venoconstriction, which causes transudation of fluid from the vascular compartments into the dependent tissues. It is dose-dependent and not responsive to diuretic therapy, and can be treatment-limiting. Oedema can slowly resolve without intervention but is alleviated adding an RAS blocker. Verapamil and diltiazem are negative inotropic and dromotropic agents, which is the basis for their use as heart rate-lowering drugs as alternatives to beta-blockers (2).

### CONTRAINDICATIONS AND PRECAUTIONS

The non-DHPs can induce severe bradycardia, impairment of sinoatrial and atrioventricular conduction and depression of contractility; therefore, they are contraindicated in patients with high-grade sinoatrial or atrioventricular block and in severe left ventricular dysfunction (8). Non-DHPs should not be combined, unless needed in selected patients with arrhythmias, with beta-blockers because of their shared negative effects on sinoatrial or atrioventricular nodes (Table 40.4).

## BETA-BLOCKERS

### MECHANISM OF ACTION

Beta-blockers are a heterogeneous group of antihypertensive agents that antagonize the effects of catecholamines at

beta-adrenoceptors (beta 1, beta 2 and beta 3) in a competitive way. Beta-blockers differ in their receptor selectivity and the presence of additional intrinsic sympathomimetic activity (ISA) (1). Beta-blockers with ISA are generally not recommended anymore. Surprisingly, the mechanisms by which beta-blockers lower BP are still not fully understood, and several modes of action are likely to be involved. A basic short-term mechanism is reducing cardiac output by their negative chronotropic and inotropic effects, which is, however, accompanied by increased peripheral resistance due to baroreceptor stimulation. Long-term lowering of BP occurs because of late lowering of peripheral vascular tone that may occur due to the resetting of baroreceptors. Other possible mechanisms include inhibition of renin secretion from the kidneys with a subsequent decrease in plasma Ang II and catecholamine levels, and a central reduction in sympathetic outflow leading to reduction in vasomotor tone. An effect on prejunctional beta receptors has also been suggested, leading to a reduction in norepinephrine release, hence adrenergic drive (2).

### CLASSIFICATION OF BETA-BLOCKERS

Currently used beta-blockers can be divided into three groups (2) (Table 40.5) based on their pharmacodynamics properties:

1. *Nonselective beta-blockers*. They block both beta 1 and beta 2 receptors without selectivity.
2. *Cardioselective beta-blockers*. They block beta 1 receptors, for example in the heart, with higher selectivity than beta 2 receptors, for example in the lung, when

**Table 40.4** Compelling and possible contraindications to the use of antihypertensive drugs

| Drug                                         | Compelling                                                                                                                                             | Possible                                                                                                                                                                          |
|----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Diuretics (thiazide/thiazide-like diuretics) | Gout                                                                                                                                                   | Metabolic syndrome<br>Glucose intolerance<br>Pregnancy<br>Hypercalcaemia<br>Hypokalaemia                                                                                          |
| Beta-blockers                                | Asthma<br>Any high-grade sinoatrial or atrioventricular block<br>Bradycardia (heart rate <60 beats/min)                                                | Metabolic syndrome<br>Glucose intolerance<br>Athletes and physically active patients<br>Chronic obstructive pulmonary disease (except for vasodilator beta-blockers)<br>Psoriasis |
| Calcium antagonists (dihydropyridines)       |                                                                                                                                                        | Tachyarrhythmia<br>Heart failure (HFrEF, class III or IV)<br>Pre-existing severe leg oedema                                                                                       |
| Calcium antagonists (verapamil, diltiazem)   | Any high-grade sinoatrial or atrioventricular block<br>Severe LV dysfunction (LV ejection fraction <40%)<br>Bradycardia (heart rate <60 beats per min) | Constipation                                                                                                                                                                      |
| ACE inhibitors                               | Pregnancy<br>Angioneurotic oedema<br>Hyperkalaemia (potassium >5.5 mmol/L)<br>Bilateral renal artery stenosis                                          | Women with childbearing potential without reliable contraception                                                                                                                  |
| Angiotensin receptor blockers                | Pregnancy<br>Hyperkalaemia (potassium >5.5 mmol/L)<br>Bilateral renal artery stenosis                                                                  | Women with childbearing potential                                                                                                                                                 |
| Mineralocorticoid receptor antagonists       | Acute or severe renal failure (eGFR < 30 mL/min/1.73 m <sup>2</sup> )<br>Hyperkalaemia                                                                 | Caution when eGFR is <45 mL/min/1.73 m <sup>2</sup>                                                                                                                               |

Abbreviation: HFrEF = heart failure with reduced ejection fraction.

used in approved doses. Overall, cardioselectivity of these drugs is still weak, dose-dependent and decreases with higher doses.

3. *Beta-blockers with additional vasodilatory effects.* Carvedilol and labetalol exhibit additional vasodilatory effects by blocking adrenergic alpha 1 receptors in arteries, while both compounds are non-selective blockers of both beta 1 and beta 2 receptors. Nebivolol is the beta-blocker with the highest beta 1 selectivity and induces its vasodilatory effect by activating nitric oxide (NO). The vasodilation enhances the BP-lowering effect of these compounds and may improve their tolerability and metabolic profile.

#### PHARMACOKINETICS AND DOSING

Wide variability exists in the pharmacokinetics of beta-blockers and their lipophilic or hydrophilic properties (3). Most of the drugs are well absorbed after oral administration; peak concentrations occur 1–3 hours after ingestion. Beta-blockers vary in the degree of elimination by the kidney or the liver. Lipophilic agents are eliminated primarily by hepatic metabolism and tend to have relatively short plasma half-lives; for example labetalol, metoprolol, pindolol and propranolol. These drugs exhibit wide interindividual variability in bioavailability and may accumulate in patients with reduced hepatic blood flow (i.e. congestive

heart failure and liver cirrhosis) (9). They cross the blood–brain barrier to a greater extent causing an increased incidence of central side effects. Hydrophilic agents are eliminated unchanged by the kidney and tend to have longer half-lives (6–24 h) and more stable plasma concentrations; e.g. atenolol and bisoprolol. They do not (or only to a small extent) cross the blood–brain barrier, and their dosage may require adjustment in renal impairment (1).

Beta-blockers are, to a varying degree, substrates of CYP450 (e.g. CYP2D6) enzymes and can therefore be affected by drug interactions (1). Compounds eliminated via metabolism in the liver (e.g. metoprolol and carvedilol) have a greater potential for drug interactions compared to compounds renally excreted such as atenolol or bisoprolol. Alcohol, phenytoin, rifampicin and phenobarbital, as well as smoking, induce hepatic CYP450 enzymes and may decrease plasma concentrations and elimination half-lives of lipophilic beta-blockers. Multiple daily dosing is required for several beta-blockers in order to provide 24-hour BP-lowering effects (9). However, slow release or long-acting formulations have been developed for some beta-blockers with short half-lives to allow once-daily dosing. Abrupt discontinuation of beta-blockers after chronic treatment should be avoided since it can lead to rebound symptoms (BP and heart rate increase, arrhythmias and angina) due to upregulation of beta adrenoreceptors during chronic treatment (1).

**Table 40.5** Pharmacokinetic characteristics and dosage of selected beta-blockers

| Drug                                                        | Half-life (h) | Daily frequency of administration | Usual dosing range (mg/day) | Renal elimination <sup>a</sup> |
|-------------------------------------------------------------|---------------|-----------------------------------|-----------------------------|--------------------------------|
| <b>Beta-blockers – Noncardioselective</b>                   |               |                                   |                             |                                |
| Nadolol                                                     | 14–24         | 1                                 | 40–120                      | >60%                           |
| Propranolol IR                                              | 3.5–6         | 2                                 | 160–480                     | –                              |
| Propranolol LA                                              | 8–11          | 1                                 | 80–320                      | –                              |
| <b>Beta-blockers – Cardioselective</b>                      |               |                                   |                             |                                |
| Atenolol                                                    | 6–9           | 1                                 | 25–100                      | 90%                            |
| Betaxolol                                                   | 14–22         | 1                                 | 5–20                        | 20%                            |
| Bisoprolol                                                  | 9–12          | 1                                 | 2.5–10                      | 52%                            |
| Metoprolol tartrate                                         | 3–4           | 2                                 | 100–400                     | <20%                           |
| Metoprolol succinate                                        | 3–7           | 1                                 | 50–200                      | <20%                           |
| <b>Beta-blockers – With additional vasodilatory effects</b> |               |                                   |                             |                                |
| Nebivolol                                                   | 11–30         | 1                                 | 5–40                        | <5%                            |
| Carvedilol                                                  | 7–10          | 2                                 | 12.5–50                     | –                              |
| Carvedilol phosphate                                        | 11            | 1                                 | 20–80                       | –                              |
| Labetalol                                                   | 5             | 2                                 | 200–800                     | <5%                            |

Abbreviations: IR, immediate release; LA, long acting.

<sup>a</sup> See Table 40.1; –, indicates almost no renal elimination.

## ADVERSE EFFECTS

In general, beta-blockers are well tolerated but can cause serious adverse effects, especially at high doses (1).

**General:** Myalgia, tiredness and fatigue due to reduced cardiac output and decreased blood flow to skeletal muscles occur mainly with nonselective agents.

**Central nervous system:** Vivid dreams, nightmares, depression, and, rarely, hallucinations, especially with highly lipid-soluble agents with greater penetration into the central nervous system.

**Cardiovascular:** Bradycardia, sinoatrial and atrioventricular block.

**Respiratory:** Wheezing, dyspnoea and bronchospasm in susceptible individuals due to blockade of beta 2 receptors, which mediate bronchodilation.

**Skin:** Can cause drug-induced or exacerbation of psoriasis and psoriasiform dermatitis.

**Sexual:** Erectile dysfunction, less common with vasodilating agents.

**Metabolic:** Weight gain, dyslipidemia, and increased insulin resistance. In patients with diabetes, beta-blockers may mask some of the warning symptoms (tremor and tachycardia) of hypoglycaemia during intensive glucose-lowering (insulin) treatment.

## CONTRAINDICATIONS AND PRECAUTIONS

The contraindications to initiate a beta-blocker include asthma and high-grade sinoatrial or atrioventricular

block. Several known precautions are overruled based on clinical judgement and tolerability when the benefit of therapy outweighs the risk of adverse effects (Table 40.4). Concomitant use with the non-DHP CCBs diltiazem and verapamil is not recommended, unless needed in selected patients with arrhythmias, due to synergistic negative effects on the sinoatrial and atrioventricular nodes. Combination with thiazide or thiazide-like diuretics leads to unfavourable lipid and glucose profiles and increases the likelihood of new-onset diabetes (2).

## DIURETICS

### THIAZIDE DIURETICS

#### MECHANISM OF ACTION

Thiazide and thiazide-like diuretics are commonly grouped together and referred to as thiazide diuretics (3). These agents promote natriuresis and diuresis depleting body stores of sodium which results in lowering of BP. They act primarily by inhibiting the Na<sup>+</sup>/Cl<sup>-</sup> cotransporter in the distal tubule of the kidney, which inhibits Na<sup>+</sup> reabsorption (1). Because this transporter only reabsorbs a small fraction (about 5%) of filtered Na<sup>+</sup>, thiazides are less potent than loop diuretics. The latter act proximally at the ascending limb of the loop of Henle (3). The effects of thiazide diuretics on BP is triphasic: (i) short term,



(ii) long term, and (iii) chronic. In the short-term phase (i.e. first 2–4 weeks), reductions in BP occur due to the decrease in plasma volume which reduces cardiac output. A countereffect elicited by consecutive rise in plasma renin and transient increase in peripheral vascular resistance opposes the BP-lowering effect. During the long-term phase, BP is still lowered due to a gradual reduction in peripheral vascular resistance, while cardiac output and plasma volume return to pretreatment levels. A chronic antihypertensive effect is reached after about 2 months due to a persistent reduction in peripheral resistance, where a new steady state of reduced total body sodium and BP is established (2).

### CLASSIFICATION

Despite their structural variation, thiazide and thiazide-like diuretics could be still considered as one group sharing a similar mode of action. Thiazide diuretics include hydrochlorothiazide and bendroflumethiazide, while indapamide, chlorthalidone and metolazone are thiazide-like diuretics (3).

### PHARMACOKINETICS AND DOSING

Thiazides are rapidly absorbed from the gastrointestinal tract and are highly bound to plasma proteins. Most of them are excreted unchanged by active secretion at the proximal tubules (1). Hepatic metabolism is almost nonexistent except for indapamide, which undergoes extensive metabolism by CYP3A4. Thiazides exert a diuretic effect within 1–3 h that lasts for 12–24 h. Chlorthalidone, indapamide and metolazone are longer-acting drugs, with a longer half-life and larger volume of distribution (due to binding to erythrocytes) than hydrochlorothiazide. Thiazides at conventional dosages are ineffective in patients with severe renal impairment ( $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ ) because the reduced GFR limits the filtered  $\text{Na}^+$  load reaching the distal tubule. In such patients, loop diuretics are preferred for management of hypertension because of their more proximal site of action. Whereas higher dosages were used in the past, e.g. 50–200 mg of hydrochlorothiazide, there was a successful development to reduce the recommended dose of thiazide-type diuretics to minimize their adverse effects. Low-dose treatment with thiazide diuretics is particularly effective in combination therapy with other antihypertensive agents, particularly RAS blockers (10). Indapamide and chlorthalidone are more potent BP-lowering agents when compared to hydrochlorothiazide on milligram basis, and provide a longer duration of action due to their greater half-lives (particularly for chlorthalidone). Despite this, their tolerability profile is not impaired.

### ADVERSE EFFECTS

Thiazides have various biochemical adverse effects that are mainly dose dependent. They share several adverse effects with beta-blockers: both drug classes may worsen glucose intolerance and dyslipidemia, particularly when combined in treatment. Thiazide diuretics decrease lithium renal excretion and increase the risk of lithium toxicity. Unlike loop diuretics, they increase renal calcium reabsorption and thus decrease calciuresis (10).

**Hypokalaemia:** Thiazides induce hypokalaemia, which may have a negative impact on their cardiac safety (cardiac

arrhythmias) and was linked to their pro-diabetic effect. The risk of hypokalaemia increases in combination with several other drugs (amphotericin B, beta 2-adrenergic agonists and loop diuretics).

**Other electrolyte disturbances:** Hypomagnesaemia, hyponatraemia and hypercalcaemia.

**Metabolic:** Hyperglycaemia and dyslipidaemia, i.e. increase in total cholesterol, low-density lipoprotein cholesterol and triglyceride levels, and decrease in high-density lipoprotein cholesterol.

**Hyperuricemia:** Thiazides, being sulphonamide-related organic acids, compete with uric acid for secretion by the same transporter (rOAT1) at the proximal tubule. This leads to increased reabsorption of uric acid and increase in serum urate levels.

### CONTRAINDICATIONS AND PRECAUTIONS

Although gout has been generally considered as a contraindication for the use of thiazide diuretics, they might be still used with caution in affected patients, particularly when thiazides are needed to control BP in otherwise high-risk resistant patients and when uric acid can be controlled by specific drug treatment (Table 40.4).

### LOOP DIURETICS

#### MECHANISM OF ACTION

Loop diuretics exert their effects at the thick ascending limb of the loop of Henle, where they inhibit  $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ -cotransporter (NKCC). Loop diuretics are more potent diuretics than thiazides, but they are shorter acting, causing reflex stimulation of the RAS, which attenuates their BP-lowering efficacy (10). Because of their pharmacodynamics and kinetic profile, they have no place in the routine management of hypertension in patients with normal renal function. They should replace thiazides, however, if  $\text{eGFR}$  is  $< 30 \text{ mL/min/1.73 m}^2$  or their use is required to control volume status of patients; e.g. with severe oedema (2).

### PHARMACOKINETICS AND DOSING

All loop diuretics are rapidly absorbed from the gastrointestinal tract, followed by extensive binding to plasma proteins. They exert their peak effect after 1–1.5 h. Oral absorption of bumetanide and torsemide is high even in patients with severe oedema so that their effects are more predictable than those of furosemide; the latter shows variable gastrointestinal absorption (3). Elimination varies also between loop diuretics (Table 40.6). Furosemide is predominantly eliminated by the kidney, while torsemide is significantly metabolized by CYP450 enzymes and eliminated by the hepatic route. Consequently, the half-life of furosemide is prolonged in advanced renal dysfunction, while the half-life of torsemide is doubled in hepatic dysfunction. Torsemide can be administered once daily (1).

### ADVERSE EFFECTS

Most of the selected adverse effects described for thiazide diuretics apply also to loop diuretics with gradual differences. A significant difference is the disparate effect on

**Table 40.6** Pharmacokinetic characteristics and dosage of selected thiazide and loop diuretics

| Drug                                       | Half-life (h) | Daily frequency of administration | Usual dosing range (mg/day) | Renal elimination (%) <sup>a</sup> |
|--------------------------------------------|---------------|-----------------------------------|-----------------------------|------------------------------------|
| <b>Thiazide and thiazide-like diuretic</b> |               |                                   |                             |                                    |
| Hydrochlorothiazide                        | 6–14          | 1                                 | 25–50                       | >90                                |
| Chlorthalidone                             | 40–60         | 1                                 | 12.5–25                     | 95                                 |
| Bendroflumethiazide                        | 3–4           | 1                                 | 1.25–5                      | 30                                 |
| Indapamide                                 | 14–18         | 1                                 | 1.25–2.5                    | 7                                  |
| Metolazone                                 | 8–24          | 1                                 | 2.5–10                      | 80                                 |
| <b>Loop diuretics</b>                      |               |                                   |                             |                                    |
| Bumetanide                                 | 1–1.5         | 2                                 | 0.5–4                       | 65                                 |
| Furosemide                                 | 1.3–3.5       | 2                                 | 20–80                       | 70                                 |
| Torsemide                                  | 3–6           | 1                                 | 5–10                        | 25                                 |

<sup>a</sup> See Table 40.1.**Table 40.7** Drugs to be preferred in specific conditions

| Indication                                    | Treatment choice                                                         |
|-----------------------------------------------|--------------------------------------------------------------------------|
| <b>Asymptomatic organ damage</b>              |                                                                          |
| LVH                                           | ACE inhibitor, calcium antagonist, ARB                                   |
| Asymptomatic atherosclerosis                  | Calcium antagonist, ACE inhibitor                                        |
| Microalbuminuria                              | ACE inhibitor, ARB                                                       |
| Renal dysfunction                             | ACE inhibitor, ARB                                                       |
| <b>Clinical CV event</b>                      |                                                                          |
| Previous stroke                               | Any agent effectively lowering BP                                        |
| Previous myocardial infarction                | BB, ACE inhibitor, ARB                                                   |
| Angina pectoris                               | BB, calcium antagonist                                                   |
| Heart failure                                 | Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonists |
| Aortic aneurysm                               | BB                                                                       |
| Atrial fibrillation, prevention               | Consider ARB, ACE inhibitor, BB or mineralocorticoid receptor antagonist |
| Atrial fibrillation, ventricular rate control | BB, non-dihydropyridine calcium antagonist                               |
| ESRD/proteinuria                              | ACE inhibitor, ARB                                                       |
| Peripheral artery disease                     | ACE inhibitor, calcium antagonist                                        |
| <b>Other</b>                                  |                                                                          |
| ISH (elderly)                                 | Diuretic, calcium antagonist                                             |
| Metabolic syndrome                            | ACE inhibitor, ARB, calcium antagonist                                   |
| Diabetes mellitus                             | ACE inhibitor, ARB                                                       |
| Pregnancy                                     | Methyldopa, BB, calcium antagonist                                       |
| Blacks                                        | Diuretic, calcium antagonist                                             |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, beta-blocker; BP, blood pressure; CV, cardiovascular; ESRD, end-stage renal disease; ISH, isolated systolic hypertension; LVH, left ventricular hypertrophy.

calcium handling with loop diuretics increasing calcium excretion (2).

### ADDITIONAL ANTIHYPERTENSIVE DRUGS

The preferred use of the drugs discussed above in specific conditions is summarized in Table 40.7. Additional drugs, that can be used in patients with treatment-resistant hypertension or other conditions are summarized in Table 40.8. The additional treatment with low-dose spironolactone (25–50 mg daily) has recently been shown to be more effective than the alpha-blocker doxazosin or beta-blocker bisoprolol when added as the fourth drug to patients with resistant hypertension already treated with a RAS-blocker, CCB, and thiazide-like diuretic (11). Centrally active drugs such as clonidine or moxonidine are less frequently used because of their poorer tolerability. Methyldopa is used because of its safety for treatment of hypertension in pregnancy. Aliskiren is the first nonpeptide, currently available orally active direct renin inhibitor (12). Because renin inhibition overcomes the reactive renin release observed during use of ACE inhibitors or ARBs, this concept was considered advantageous when targeting the RAS. However, during late-stage clinical development, aliskiren was predominantly studied on top of treatment with another RAS-blocker (i.e. during dual RAS blockade), and these trials generated unfavourable results.

Consequently, further research with this compound was halted, and currently no trials are available on cardiovascular or renal outcome events in hypertension that support its use. Direct-acting vasodilators are a heterogeneous group of drugs, among which hydralazine and minoxidil are most frequently used. Their use is associated with tachycardia and fluid retention and other significant side effects, and thus use is restricted to special conditions.

### DEVELOPMENT OF NOVEL ANTIHYPERTENSIVE DRUGS

Although effective antihypertensive agents are available on the market, hypertension is still not sufficiently controlled in a majority of patients. There is a need for effective treatment strategies in patients with resistant hypertension, those with comorbidities, or patients intolerant to the available drugs. In addition to the drugs mentioned in this chapter, several novel drugs for the treatment of hypertension or associated diseases are currently being developed at either the preclinical or clinical stage. These new agents with novel targets have applications that may extend beyond protection against cardiovascular diseases and target-organ damage. A summary of the compounds and their status of development is given in Table 40.9; further details were recently reported (13).

**Table 40.8** Summary of selected additional antihypertensive agents

| Drug class/subclass                                                                                                                | Mode of action                                                                                                                                                              | Dosage (mg/day)                       | Adverse effects                                                                                                         |
|------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| <b>Potassium-sparing diuretics/Mineralocorticoid receptor antagonists</b><br>■ Spironolactone<br>■ Eplerenone                      | Block aldosterone receptor in distal tubule in the kidney leading to natriuresis and potassium retention                                                                    | 25–50<br>25–50                        | Hyperkalaemia, worsening renal function, metabolic acidosis, gynecomastia, impotence                                    |
| <b>Potassium-sparing diuretics</b><br>■ Amiloride                                                                                  | Blocks directly the epithelial sodium channel (ENaC) within the distal tubule of the kidney natriuresis and potassium retention                                             | 5–10                                  | Hyperkalaemia, abdominal pain, nausea                                                                                   |
| <b>Alpha blockers</b><br>■ Doxazosin<br>■ Terazosin                                                                                | Decrease peripheral vascular resistance by selective blockade of $\alpha_1$ adrenoceptors                                                                                   | 1–8<br>1–20                           | Fluid retention, orthostatic hypotension especially in older adults                                                     |
| <b>Direct-acting vasodilators</b><br>■ Minoxidil<br>■ Hydralazine                                                                  | Hyperpolarization of smooth muscle membrane through opening of potassium channels<br>Direct vasodilation of resistance arterioles by increasing NO synthesis in endothelium | 5–100<br>250–200                      | Fluid retention, reflex tachycardia<br>Hypertrichosis – with Minoxidil<br>Risk of drug-induced lupus – with hydralazine |
| <b>Centrally acting sympatholytic agents/Alpha-2 agonist</b><br>■ Clonidine<br>■ Moxonidine<br>■ Rilmenidine<br>■ Alpha-Methyldopa | Reduce sympathetic outflow centrally by stimulating presynaptic $\alpha_2$ receptors and/or imidazoline receptors                                                           | 0.1–0.8<br>0.2–0.4<br>1–2<br>500–2000 | Bradycardia, somnolence, dry mouth                                                                                      |
| <b>Direct renin inhibitor</b><br>■ Aliskiren                                                                                       | Reduces plasma renin activity with subsequent reduction of angiotensin I and angiotensin II                                                                                 | 150–300                               | Diarrhea, cough, changes in renal function                                                                              |

Abbreviation: NO, nitric oxide.

**Table 40.9** Selected novel drugs in the treatment of hypertension and their status of development

| Therapeutic group/<br>category                                                                      | Mechanism of action                                                                                                        | Drug/compound                                                   | Status                                                         | Selected clinical<br>trial number                                                      | Pharmaceutical<br>industry/<br>developer            |
|-----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------------|
| <b>ACE2 activator</b>                                                                               | Activating RAS counter-regulatory system                                                                                   | APN01 (rhACE2)<br>GSK 2586881<br>(rhACE2)                       | Phase I<br>Phase II                                            | NCT00886353<br>NCT01597635                                                             | Apeiron Biologics<br>GlaxoSmithKline                |
| <b>Mineralocorticoid<br/>receptor antagonist</b>                                                    | Anti-aldosterone effect                                                                                                    | BAY 94–8862<br>(Finerenone)                                     | Phase II <sup>b</sup><br>Phase III <sup>a</sup>                | NCT01807221<br>NCT01874431<br>NCT02540993<br>NCT02545049                               | Bayer HealthCare                                    |
| <b>Neprilysin inhibitor</b>                                                                         | Blockade of natriuretic<br>peptide system                                                                                  | TD-0714                                                         | Phase I                                                        | NCT02709928                                                                            | Theravance<br>Biopharma                             |
| <b>Dual-acting<br/>angiotensin<br/>receptor-neprilysin<br/>inhibitor</b>                            | Dual blockade of RAS and<br>the natriuretic peptide<br>system                                                              | LCZ696 (Sacubitril/<br>Valsartan)                               | Approved<br>Phase III<br>Phase IV                              | NCT00549770<br>NCT01785472<br>NCT01920711<br>NCT02690974<br>NCT02754518<br>NCT02887183 | Novartis<br>Pharmaceuticals                         |
| <b>Dual acting<br/>endothelin-<br/>converting<br/>enzymes-neprilysin<br/>inhibitor</b>              | Dual blockade of the<br>natriuretic peptide system<br>and endothelin<br>-1-mediated<br>vasoconstriction                    | SLV-306 (Daglutril)                                             | Phase II                                                       | NCT00160212<br>NCT00160225                                                             | Solvay<br>Pharmaceuticals                           |
| <b>Vasoactive intestinal<br/>peptide receptor 2<br/>(VPAC2) agonist</b>                             | Vasodilation                                                                                                               | PB1046 (Vasomera)                                               | Phase I<br>Phase II                                            | NCT01523067<br>NCT01873885<br>NCT02808585                                              | PhaseBio<br>Pharmaceuticals Inc.                    |
| <b>Nitric oxide donor</b><br>■ CINOD<br>■ Soluble Guanylate<br>cyclase stimulator                   | Vasodilation                                                                                                               | AZD 3582<br>(Naproxcinod)<br>YC-1<br>BAY-63-2521<br>(Riociguat) | Phase III <sup>b</sup><br>Preclinical<br>Phase III<br>Phase II | NCT00662896<br>n.a.<br>NCT00810693<br>NCT00863681<br>NCT02744339                       | NicOx<br>—<br>Bayer-HealthCare                      |
| <b>Intestinal Na<sup>+</sup>/H<sup>+</sup><br/>exchanger 3<br/>inhibitor</b>                        | Impaired intestinal sodium<br>absorption                                                                                   | AZD1722 (Tenapanor)<br>SAR218034                                | Phase II<br>Preclinical                                        | NCT01847092<br>NCT02675998<br>n.a.                                                     | Ardelyx<br>—                                        |
| <b>Vaccine against<br/>angiotensin II</b>                                                           | Blockade of RAS                                                                                                            | CYT006-AngQβ<br>AngII-KLH<br>pHAV-4AngII                        | Phase II<br>Preclinical<br>Preclinical                         | NCT00500786<br>n.a.<br>n.a.                                                            | Cytos Biotechnology<br>AG<br>—                      |
| <b>Pre-eclampsia drugs</b><br>■ Anti-digoxin antibody<br>fragment<br>■ Recombinant<br>anti-thrombin | Reduction of endogenous<br>digitalis-like factors<br>elevated in pre-eclampsia<br>Reduction of thrombin and<br>proteinuria | DIF<br>ATryn                                                    | Phase II<br>expedited<br>Phase III                             | NCT00158743<br>NCT02059135                                                             | BTG; Glenveigh<br>Pharmaceuticals<br>rEVO Biologics |

Abbreviations: NCT, indicates the clinical trial number registered at ClinicalTrials.gov; n.a., not applicable; CINOD, cyclo-oxygenase-inhibiting nitric-oxide donor.

<sup>a</sup> In diabetic kidney disease.

<sup>b</sup> In arthritis.

## REFERENCES

- Benowitz N. Antihypertensive agents. In: Katzung BG, Trevor, AJ (eds). *Basic & Clinical Pharmacology*. 13th ed. McGraw-Hill Education, New York; 2015: 169–190.
- Laurent S. Antihypertensive drugs. *Pharmacol Res* 2017; 124: 116–125.
- Michel T, Hoffman B. Treatment of myocardial ischemia and hypertension. In: Brunton LCB, Knollmann B (eds). *Goodman & Gilman's the Pharmacological Basis of Therapeutics*. 12th ed. McGraw-Hill, New York; 2011: 745–788.
- Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31(7): 1281–1357.
- Song JC, White CM. Clinical pharmacokinetics and selective pharmacodynamics of new angiotensin converting enzyme inhibitors: An update. *Clin Pharmacokinet* 2002; 41(3): 207–224.
- <http://dosing.de/>. Accessed March 2018.

7. Unger T. Pharmacological properties of angiotensin II antagonists: Examining all the therapeutic implications. *JRAAS* 2001; 2(Suppl 2): S4–S7.
8. Godfraind T. Discovery and development of calcium channel blockers. *Front Pharmacol* 2017; 8: 286.
9. Frishman WH, Alwarshetty M. Beta-adrenergic blockers in systemic hypertension: Pharmacokinetic considerations related to the current guidelines. *Clin Pharmacokinet* 2002; 41(7): 505–516.
10. Brater DC. Diuretic therapy. *N Engl J Med* 1998; 339(6): 387–395.
11. Williams B, MacDonald TM, Morant S et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): A randomised, double-blind, crossover trial. *Lancet (London)* 2015; 386(10008): 2059–2068.
12. Rahuel J, Rasetti V, Maibaum J et al. Structure-based drug design: The discovery of novel nonpeptide orally active inhibitors of human renin. *Chem Biol* 2000; 7(7): 493–504.
13. Kreutz R, Algharably E. Novel drugs in the treatment of hypertension. In: Tsioufis C, Schmieder R, Mancia G (eds). *Updates in Hypertension and Cardiovascular Protection*. Springer, Switzerland; 2016: 157–178.





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# SINGLE-PILL COMBINATION TREATMENTS IN HYPERTENSION

# 41

Michel Burnier

## INTRODUCTION

High blood pressure (BP) remains a leading cause of mortality and cardiovascular and renal complications despite all the efforts made during the last decades to improve BP control. Although the prevalence of elevated BP has decreased between 1975 and 2015 mainly in high-income countries, the number of adults with raised BP has increased steadily over time worldwide, to reach more than 1 billion adults affected in 2015, due in part to the ageing of populations (1). One big issue with this enormous burden of subjects with elevated BP is that a large percentage of them are not aware of being hypertensive and, among those who are aware, only few are well controlled. Thus, in 2010, only 50.4% of hypertensive patients from high-income countries had their BP under control, whereas in middle- and low-income countries this figure was only 26.3% and in regression when compared to 2000 (2). Unfortunately, patients with a poorly controlled BP remain at high risk of developing cardiovascular complications.

This rather disappointing control of BP in populations contrasts with the results obtained in clinical studies. Indeed, in almost all hypertensive conditions, antihypertensive drugs lower BP and reduce cardiovascular morbidity and mortality. Moreover, in most large clinical trials, close to 80% of enrolled hypertensive patients usually reach the predefined BP targets (3). These observations suggest that antihypertensive drugs available today are effective in lowering BP but that there is a clear gap between the context of a clinical study and the real-life management of patients with hypertension. Several factors may explain this discrepancy, such as medical inertia, poor adherence to the prescribed therapy or deficiencies in healthcare systems (4). A high pill burden might also potentially contribute to this gap, limiting the persistence on therapy (5). Indeed, in earlier hypertension guidelines, the recommendation was to initiate the treatment of hypertension based on the stepped care principle. Patients were started on a monotherapy and additional drugs were added gradually whenever BP was failing to normalize. This approach had obvious limitations, in particular among patients with complex diseases and multiple therapies. This led to the re-evaluation of the use of fixed-dose combinations rather than multiple single drugs to simplify the treatment

regimen and increase its efficacy (6). In fact, fixed combinations of antihypertensive drugs were already used in the early 1960s, but with drugs that are not prescribed anymore, except perhaps for the fixed association of an aldosterone antagonist and a thiazide (7,8). Later, however, the step-by-step addition of monotherapies was preferred over drug combinations in practice.

## RATIONALE FOR SINGLE-PILL COMBINATIONS IN HYPERTENSION

There are several physiological, pharmacological and clinical reasons to the use of single-pill combinations in the management of hypertension (Table 41.1), and these are discussed below.

Firstly, hypertension is a multifactorial disease caused in the majority of cases by dysregulations of several mechanisms implicated in the regulation of BP (9). Thus, the likelihood that BP will be normalized using a single drug class targeting only one regulatory system is low, unless patients suffer from a monogenic form of hypertension. In accordance with this observation, only about 30–40% of hypertensive patients are controlled with monotherapy (10).

Secondly, the dose-response curve of most antihypertensive drugs is relatively flat (11). Therefore, increasing the dose of monotherapies to or above the maximal recommended doses is expected to provide little if any additional antihypertensive benefit and definitively less than combining drugs from different classes (12). As supported by the analysis of Wald et al. BP reduction from combining drugs from two different classes is significantly greater than doubling the dose of one drug (Figure 41.1) (12). However, per se, combining drug classes with a different mechanism of action is not sufficient. Indeed, the drug combination should have a synergistic effect on BP as well as on the ability to protect against target-organ damage without increasing the risk of complications. Increasing the dose of antihypertensive drugs is generally associated with a higher incidence of side effects, an observation which has been made with all drug classes except angiotensin receptor antagonists (ARB) (11). As discussed later in this chapter, combining drugs with different

**Table 41.1** Advantages and disadvantages of the use of single-pill combinations in hypertension

| Advantages                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>■ Reduction of the pill burden</li> <li>■ Simplification of the treatment schedule</li> <li>■ Increased adherence to therapy (better long-term persistence)</li> <li>■ Improved efficacy with reduced incidence of side effects</li> <li>■ Faster reduction in blood pressure</li> <li>■ Better prevention of cardiovascular events (to be demonstrated prospectively)</li> <li>■ Better acceptance by patients</li> <li>■ Reduce cost of hypertension management</li> </ul>    |
| Disadvantages                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <ul style="list-style-type: none"> <li>■ Reduction of prescription flexibility</li> <li>■ Difficult to identify the precise cause of an unexpected side effect</li> <li>■ Difficult to memorize the exact content of the single-pill combinations</li> <li>■ Risk of a more pronounced rebound hypertension in case of repeated omissions</li> <li>■ Risk of acute hypotension when restarting a triple combination after interruptions</li> <li>■ Increased drug cost versus free combinations of generics</li> </ul> |

mechanisms decreases rather than increases the incidence of side effects. Taking into account these arguments, it is preferable to use single-pill combinations containing drug classes with different but complementary mechanisms of action rather than free-drug monotherapies if one wishes to increase BP control in a larger percentage of the hypertensive population.

Thirdly, there are several clinical arguments to encourage a wider use of single-pill combinations in hypertension. In this respect, one should mention the reduction of the pill burden, which has been associated with an improvement of long-term adherence to prescribed medications. As mentioned previously, adherence to prescribed

drug therapies is a major issue in hypertension (5). Several studies and meta-analyses have now confirmed the advantage of prescribing single-pill combinations rather than free-drug combinations to reduce the risk of nonadherence by about 25% and hence increase long-term persistence with antihypertensive regimens (13–15) (Figure 41.2). However, it must be emphasized that these meta-analyses were conducted on a rather small number of clinical studies, and methods assessing drug adherence in these studies were not always the most adequate. In terms of adherence and efficacy, the duration of action of each component of the combination is very important. In order to cover for occasionally missed doses and to lower the cardiovascular risk, the ideal single-pill combination should associate two drugs with a long duration of action (16).

Another important argument for the use of single-pill combinations is that many subgroups of hypertensive patients such as elderly patients or patients with chronic kidney disease or type 2 diabetes need more than two drugs to lower their BP to target. In addition, in these patients with a high cardiovascular risk, the decrease in BP is more rapid, and this may have a positive impact on the patients' risk of developing cardiovascular complications (17). If the cost of single-pill combinations is often superior to that of generic compounds, studies have nevertheless shown that the use of single-pill combinations may be globally more cost-effective than the use of free-drug combinations (15,18).

Finally, combining therapeutic strategies offers advantages on the development of side effects. This was actually the principle of the initial concept of fixed *low-dose* combinations, according to which combining a low dose of two therapeutic agents has a greater antihypertensive efficacy but induces fewer side effects than a high-dose monotherapy. With the greatly improved tolerability profile of newer antihypertensive drugs such as angiotensin receptor blockers, the concept of low-dose combinations was progressively abandoned in favour of high-dose single-pill combinations. In this respect, when combining therapeutic strategies, each component has the potential of neutralizing counterregulatory mechanisms and thereby of reducing the development of potential side effects while the BP-lowering effect of each component of the combination is enhanced. One good example of such a synergism is the association of a blocker of the renin–angiotensin system (RAS) and a thiazide diuretic. The thiazide-induced natriuresis potentiates the antihypertensive efficacy of RAS blockers stimulating renin, whereas RAS blockers limit the kaliuresis induced by the thiazide diuretic and therefore limit the incidence of hypokalaemia (19). Among other examples, one can cite the reduction of the incidence of peripheral oedema with calcium channel blockers (CCBs) when these latter are associated with an RAS blocker (20) or the prevention of the dihydropyridine-induced tachycardia with the association of a beta-blocker.

Single-pill combinations of antihypertensive drugs have also some limitations. In some countries, fixed-dose combinations are still much more expensive than generics of free-drugs and cannot always be prescribed by general practitioners. In addition, the duration of action of individual components may not be equivalent, thereby not justifying a single daily dosing of the combination. The use of fixed-dose combinations may result in less flexibility in modifying the doses of individual components, despite the availability of many dosages for many

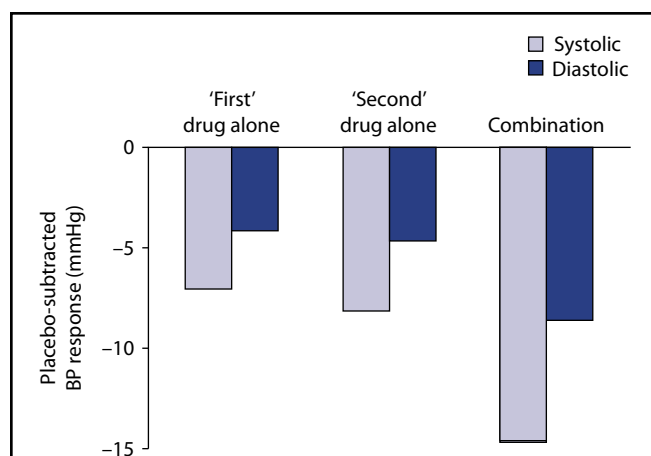


**Figure 41.1** Blood pressure response (after subtraction of the placebo effect) to two different drugs administered separately and in combination, based on the observations made in randomized placebo-controlled trials. (Data from Wald et al. *Am J Med* 2009; 122(3): 290–300.)

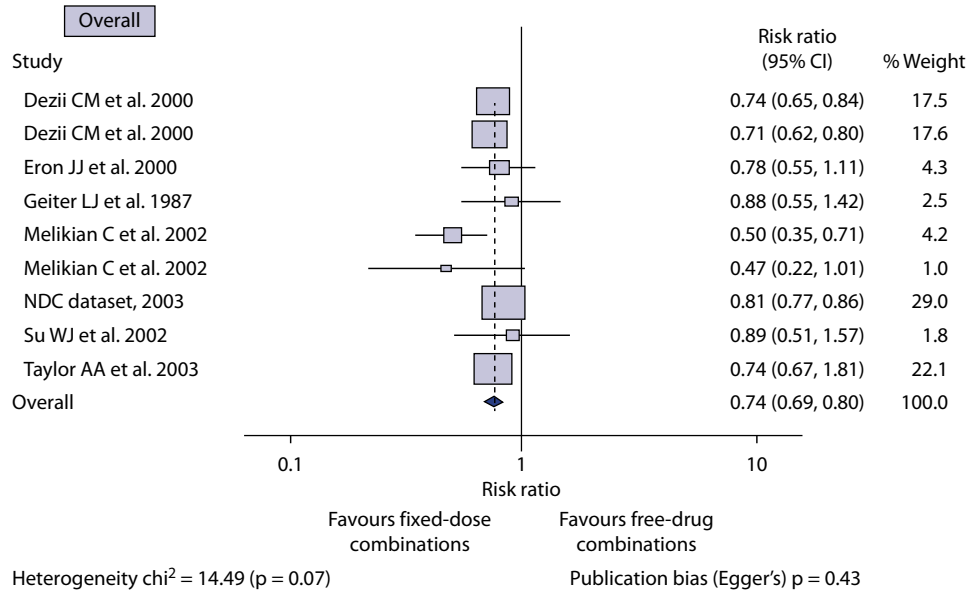


**Figure 41.2** Effect of fixed-dose combination versus free-drug combination on the risk of noncompliance to medication regimens. Complete references of publications indicated in the figure can be found in the original paper by Bangalore et al. (From Bangalore S et al. *Am J Med* 2007; 120(8): 713–719.)

single-pill combinations. When nonspecific side effects occur, it may become more difficult to identify which component of the combination is responsible. Finally, one may expose patients with a low cardiovascular risk to unnecessary therapy when prescribing single-pill combinations as first-line therapies (21), and there is a risk of hypotension if patients miss several doses and restart, for example, on a triple combination.

## SINGLE-PILL DUAL COMBINATIONS

Today, there is a very large choice of single-pill combinations associating two antihypertensive drug classes available on the market. They generally combine drug classes recommended as first-line therapy by international guidelines such as diuretics, beta-blockers, CCBs and RAS blockers (angiotensin-converting enzyme inhibitors [ACEi] or angiotensin receptor blockers [ARB]) (22). Combinations including centrally active drugs are also available in some countries.

Each of these single-pill combinations has a good rationale to justify its use in clinical practice. Thus the association of a potassium-sparing diuretic (spironolactone, amiloride or triamterene) with a thiazide diuretic enables one to limit the potassium losses and the thiazide-induced hypokalaemia. The correction of hypokalaemia may reduce the risk of cardiac and metabolic complications and sexual impotence, which is in part mediated by the thiazide-induced hypokalaemia (23), and limit the benefits of lowering BP (24). Clinically, the association of diuretics has been found to be equally effective in reducing cardiovascular events as a CCB-based therapy (nifedipine GITS) (25). A recent study in patients with resistant hypertension has suggested that combining diuretics is also a useful

approach to improve BP control by reducing the compensatory sodium reabsorption in the distal segments of the nephron (26). However, associations of diuretics containing a potassium-sparing agent must be used cautiously in patients with reduced renal function and should not be prescribed to patients with severe renal insufficiency or pre-existing hyperkalaemia.

Today, dual combinations containing an RAS blocker and a diuretic (thiazide, chlorthalidone, indapamide) belong to the most frequently used associations in the management of hypertension. There is strong physiological rationale for this association. Indeed, the negative sodium balance induced by the diuretic triggers the release of renin and the production of angiotensin II. Hence the maintenance of BP becomes angiotensin II-dependent. In this context, blockade of the reactive activation of the RAS enhances the BP-lowering effect of diuretics. Conversely, the diuretic-induced stimulation of aldosterone leading to hypokalaemia is blunted with the administration of the RAS blocker, therefore preserving an intact potassium balance (19,27). This combination is generally well tolerated, and several studies have demonstrated that the association of an RAS blocker and a diuretic is superior to a high dose of the RAS blocker alone to lower BP. Recently, the issue of which is the best diuretic has been the topic of some discussions. Indeed, there is some clinical evidence that chlorthalidone reduces cardiovascular events in hypertension better than hydrochlorothiazide (HCTZ) (28), and differences in potency between HCTZ and chlorthalidone in favour of the latter have been clearly demonstrated (29). However, almost all combinations associate an RAS blocker with low doses of HCTZ except for azilsartan, which has been developed in association with chlorthalidone, and perindopril, which is associated with low doses of indapamide (30,31). This latter is effective in lowering BP (32) and/or preventing cardiovascular events

(30). Recent comparative studies have shown that the SPC of azilsartan medoxomil and chlorthalidone induces a greater fall in 24-h ambulatory BP than azilsartan/HCTZ (33) or olmesartan/HCTZ (34) (Figure 41.3).

In recent years, the combination of an RAS blocker and a CCB in a single pill has become very popular. The main advantage of this combination is that the coadministration of the RAS blocker significantly reduces the incidence of peripheral oedema induced by the CCB (35,36). The sudden enthusiasm for this combination comes essentially from the results of the ACCOMPLISH trial (Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension), which compared the fixed combination of benazepril/amlodipine to the fixed association of benazepril/HCTZ. Despite a similar reduction in BP, the former was superior in reducing cardiovascular as well as renal events in high cardiovascular risk patients (37,38). In this trial, the benazepril/amlodipine single-pill combination reduced the relative risk of cardiovascular events by 20% and the relative risk of progression of chronic kidney disease by 48%. The clinical benefits of combining an RAS blocker and a CCB in a single pill were also supported by the results of the INVEST [INternational VErapamil SR- Trandolapril] and ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) trials (39,40). These two trials did not use fixed-dose combinations but compared the efficacy and clinical benefits of a therapeutic strategy based on an CCB as first-line therapy and an RAS blocker as the second line of treatment to the older strategy starting with a beta-blocker as first-line therapy and diuretic as second-line. The INVEST trial assessed the clinical benefits of the verapamil SR  $\pm$  trandolapril on cardiovascular events in patients with coronary heart disease, and the control group received atenolol  $\pm$  HCTZ. Both strategies were equally effective in terms of prevention of cardiovascular events but there were fewer new cases of diabetes in the verapamil/trandolapril group. The

ASCOT trial compared an amlodipine-based therapy to an atenolol-based therapy with the possibility to add perindopril to amlodipine and HCTZ to atenolol. The CCB-RAS blocker association was superior in preventing cardiovascular events and reducing cardiovascular mortality. Since then, several other single-pill combinations associating an ACE inhibitor or an ARB or a renin inhibitor with amlodipine or another CCB such as lercanidipine have been launched for the treatment of hypertension (20).

These trials may suggest that the CCB/RAS blocker combination is superior to the traditional association of RAS blocker or beta-blocker with a diuretic. However, one has to consider the characteristics of patients enrolled in these studies before extrapolating the results to the entire hypertension population. Thus, although these studies were conducted in high cardiovascular risk patients, the ACCOMPLISH trial included essentially patients of African American origin. Thus, the results of ACCOMPLISH may not be applicable to all populations around the world. In one study conducted in elderly patients with hypertension, the combination of an ARB + CCB was reported to be as effective as the same ARB + diuretic to control BP and to prevent cardiovascular events, although fewer patients developed side effects with the ARB + CCB combination (41). Another Japanese study compared the combinations of a CCB plus an ARB or a diuretic or a beta-blocker and reported no significant difference between the three combinations in terms of BP control and prevention of cardiovascular complications (42,43). In another set of experiments, Stergiou et al. examined the additional BP-lowering effect of adding a diuretic, a CCB or an ACE inhibitor on top of an ARB in patients uncontrolled with the maximal dose of the ARB alone (44). Although all three drugs added to the ARB lowered BP, only the addition of the CCB or the diuretic induced a significant decrease in BP, enabling an increase in the percentage of patients under control. This observation further confirms the initial hypothesis that combining drugs with different modes of action is preferable to an increase in dose or combining drugs acting on the same mechanism of BP control. In this respect, one has to mention that combining an ACE inhibitor and an ARB or a renin inhibitor is no longer recommended by guidelines because of the increased risk of acute renal failure and hyperkalaemia, as observed in the ONTARGET trial (4,45).

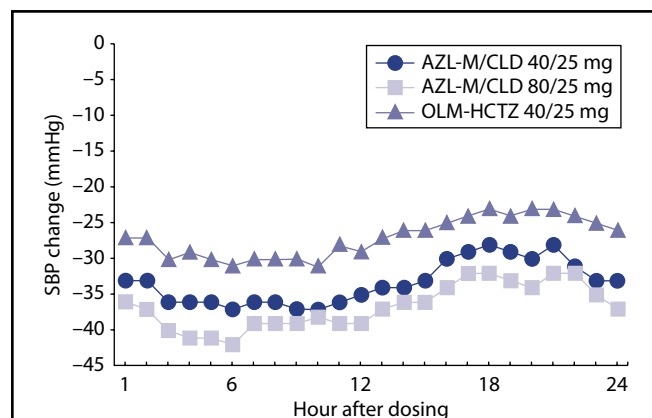


**Figure 41.3** Change from baseline in systolic blood pressure (SBP) by ambulatory blood pressure monitoring at each hour at week 12. Data are mean changes from baseline. AZL-M indicates azilsartan medoxomil/chlorthalidone; OLM/HCTZ indicates olmesartan/hydrochlorothiazide. Both AZL-M/CLD groups led to statistically significantly greater SBP reduction than OLM/HCTZ at each hour after dosing ( $P < 0.001$ ). (From Cushman WC et al. *Hypertension* 2012; 60(2): 310–318.)

## SINGLE-PILL TRIPLE COMBINATIONS

About 30–40% of patients with hypertension will need more than two drugs to achieve BP targets. These include patients with more severe forms of hypertension or resistant hypertension and those with comorbidities such as chronic kidney disease, type 2 diabetes or sleep apnoea syndrome. Ideally, patients should be able to stay on the same therapeutic scheme, increasing from a monotherapy to a triple therapy while staying on a single pill per day (46). A new paradigm has therefore emerged with the development of single-pill combination containing an RAS blocker (ACE inhibitor, ARB or aliskiren), a CCB (generally amlodipine) and a diuretic (HCTZ or indapamide) (18,47) (Table 41.2). Clinical studies have demonstrated that these triple combinations in a single pill effectively reduce BP in patients uncontrolled on a bi-therapy either as fixed or as free combinations (48–53). The prescription



**Table 41.2** Triple combinations in a single pill available in Europe

| Triple combinations          |                     |                   |                       |
|------------------------------|---------------------|-------------------|-----------------------|
| ARB/CCB/diuretic             | Valsartan (160/320) | Amlodipine (5/10) | HCTZ (12.5/25)        |
|                              | Olmesartan (20/40)  | Amlodipine (5/10) | HCTZ (12.5/25)        |
|                              | Telmisartan (40/80) | Amlodipine (5/10) | HCTZ (12.5/25)        |
| ACE inhibitor/CCB/diuretic   | Perindopril (5/10)  | Amlodipine (5/10) | Indapamide (1.25/2.5) |
| Renin inhibitor/CCB/diuretic | Aliskiren (150/300) | Amlodipine (5/10) | HCTZ (12.5/25)        |

of triple combinations should therefore be encouraged to intensify the treatment of patients with uncontrolled BP on a well-dosed bi-therapy or to simplify the therapeutic regimen in patients receiving triple free-drug combinations. One advantage of these triple combinations is the ability to progressively increase the treatment while staying on the same initial drugs in different clinical conditions associated with hypertension, as suggested recently by Volpe et al. (54). In general, patients are reassured of continuing drugs that they know they tolerated.

### THE QUARTER-DOSE QUADRUPLE COMBINATION THERAPY CONCEPT

Australian investigators have recently developed the concept of the *quadpill*, which consists of combining four active antihypertensive substances at very low dose in a single pill. This principle has been evaluated in a randomized, double-blind placebo-controlled, crossover study published in 2017 (55). The quadpill contained 37.5 mg irbesartan, 1.25 mg amlodipine, 6.25 mg hydrochlorothiazide and 12.5 mg atenolol. The primary endpoint of the study was the decrease in 24-h ambulatory BP at 4 weeks. Only a small number of 18 patients with hypertension were enrolled in this crossover study. After correction for the placebo effect, systolic ambulatory BP decreased by 19 mmHg. At baseline, 24-h ambulatory BP was 154/90 mmHg,

and all patients on the quadpill reached the target BP of <140/90 mmHg, whereas under placebo only three participants were well controlled. Side effects were more frequent with the quadpill, but they were relatively mild and only one patient stopped the quadpill. A small meta-analysis of clinical studies having investigated combinations of quarter doses previously accompanied the study. This analysis showed a range of BP decrease of 5/2–7/5 mmHg systolic/diastolic BP. A second analysis by the same authors confirmed these figures (56) (Figure 41.4), suggesting that only a combination of four drugs at very low dose (1/4) is superior to a monotherapy. This new concept may be of interest but its position in the management of hypertensive patients remains to be defined in a larger number of patients. Thus far, the dataset is small, few patients have been treated and for a short period of time. Several questions remain unanswered with this approach, such as the strategy to adopt in the case of intolerance to one of the compounds, even at low dose, or the next treatment step if BP remains uncontrolled. Whether the quadpill is superior to a dual fixed low-dose combination should also be investigated.

### SINGLE-PILL COMBINATIONS IN HYPERTENSION GUIDELINES

For many decades, recommendations for the initiation of antihypertensive treatments were to start with

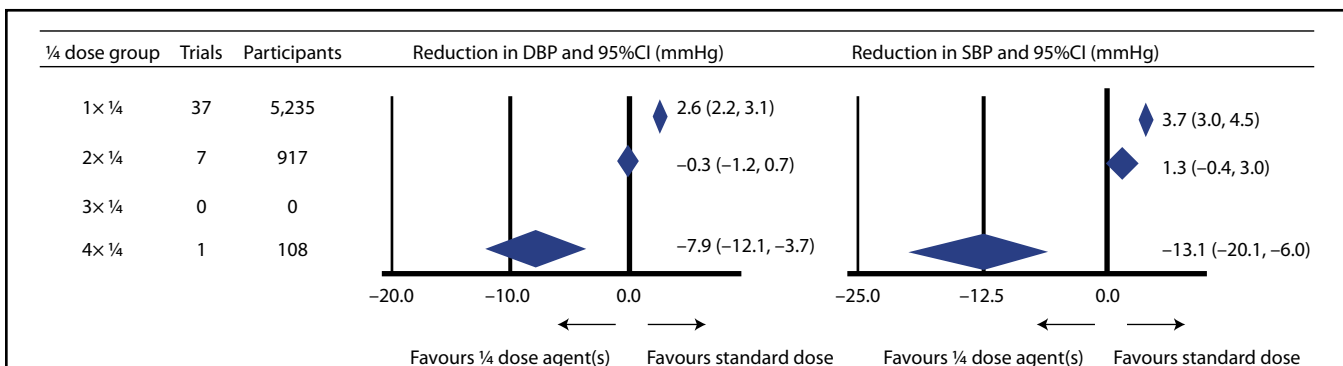


**Figure 41.4** Comparisons of single, dual, and quadruple quarter-dose therapy compared with standard-dose monotherapy on blood pressure reductions. Single quarter-dose therapy was less efficacious than standard-dose monotherapy; dual quarter-dose therapy showed an equivalent blood pressure-lowering effect compared with standard-dose monotherapy. Only one study with quadruple quarter-dose therapy versus standard-dose monotherapy showed a substantially greater blood pressure reduction in the quarter-dose group. (From Bennett A et al. *Hypertension* 2017; 70(1): 85–93.)

a monotherapy to avoid having patients who responded adequately to a single drug taking more pharmacological agents than necessary. This approach changed in the 2013 ESH/ESC hypertension guidelines with the possibility to start on a combination therapy in patients with a high cardiovascular risk or in patients with elevated baseline BP (57). Today, even this approach is questioned, and some experts suggest that there is a need to readdress the approach to antihypertensive treatment owing to the poor BP control rate worldwide. In their view, antihypertensive fixed-dose combinations should be prescribed earlier, including as first line in patients with a low cardiovascular risk and mild forms of hypertension. This new strategy is now under discussion, as it might help to shrink the current gap between antihypertensive use and BP target control achieved.

## REFERENCES

1. Collaboration NCDRF. Worldwide trends in blood pressure from 1975 to 2015: A pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* 2017; 389(10064): 37–55.
2. Mills KT, Bundy JD, Kelly TN et al. Global disparities of hypertension prevalence and control: A systematic analysis of population-based studies from 90 countries. *Circulation* 2016; 134(6): 441–450.
3. Burnier M. Blood pressure control and the implementation of guidelines in clinical practice: Can we fill the gap? *J Hypertens* 2002; 20(7): 1251–1253.
4. Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31(7): 1281–1357.
5. Burnier M, Wuerzner G, Struijker-Boudier H, Urquhart J. Measuring, analyzing, and managing drug adherence in resistant hypertension. *Hypertension* 2013; 62(2): 218–225.
6. Brunner HR, Menard J, Waeber B et al. Treating the individual hypertensive patient: Considerations on dose, sequential monotherapy and drug combinations. *J Hypertens* 1990; 8(1): 3–11; discussion 13–19.
7. Veterans Administration. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *JAMA* 1967; 202(11): 1028–1034.
8. Weir MR, Bakris GL. Combination therapy with renin-angiotensin-aldosterone receptor blockers for hypertension: How far have we come? *J Clin Hypertens (Greenwich)* 2008; 10(2): 146–152.
9. Padmanabhan S, Caulfield M, Dominiczak AF. Genetic and molecular aspects of hypertension. *Circ Res* 2015; 116(6): 937–959.
10. Turnbull F, Neal B, Algert C et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: Results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005; 165(12): 1410–1419.
11. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: Analysis of 354 randomised trials. *BMJ* 2003; 326(7404): 1427.
12. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: Meta-analysis on 11,000 participants from 42 trials. *Am J Med* 2009; 122(3): 290–300.
13. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: A meta-analysis. *Am J Med* 2007; 120(8): 713–719.
14. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: A meta-analysis. *Hypertension* 2010; 55(2): 399–407.
15. Sherrill B, Halpern M, Khan S et al. Single-pill vs free-equivalent combination therapies for hypertension: A meta-analysis of health care costs and adherence. *J Clin Hypertens (Greenwich)* 2011; 13(12): 898–909.
16. Burnier M, Brede Y, Lowy A. Impact of prolonged antihypertensive duration of action on predicted clinical outcomes in imperfectly adherent patients: Comparison of aliskiren, irbesartan and ramipril. *Int J Clin Pract* 2011; 65(2): 127–133.
17. Weber MA, Julius S, Kjeldsen SE et al. Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE Trial. *Lancet* 2004; 363(9426): 2049–2051.
18. Ram CV. Fixed-dose triple-combination treatments in the management of hypertension. *Manag Care* 2013; 22(12): 45–55.
19. Kochar M, Guthrie R, Triscari J et al. Matrix study of irbesartan with hydrochlorothiazide in mild-to-moderate hypertension. *Am J Hypertens*. 1999; 12(8 Pt 1): 797–805.
20. Burnier M, Vuignier Y, Wuerzner G. State-of-the-art treatment of hypertension: Established and new drugs. *Eur Heart J* 2014; 35(9): 557–562.
21. Angeli F, Reboldi G, Mazzotta G et al. Fixed-dose combination therapy in hypertension: Cons. *High Blood Press Cardiovasc Prev* 2012; 19(2): 51–54.
22. Waeber B, Feihl F, Ruilope LM. Fixed-dose combinations as initial therapy for hypertension: A review of approved agents and a guide to patient selection. *Drugs* 2009; 69(13): 1761–1776.
23. Alderman MH, Piller LB, Ford CE et al. Clinical significance of incident hypokalemia and hyperkalemia in treated hypertensive patients in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension* 2012; 59(5): 926–933.
24. Franse LV, Pahor M, Di Bari M et al. Hypokalemia associated with diuretic use and cardiovascular events in the Systolic Hypertension in the Elderly Program. *Hypertension* 2000; 35(5): 1025–1030.
25. Brown MJ, Palmer CR, Castaigne A et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 2000; 356(9227): 366–372.
26. Bobrie G, Frank M, Azizi M et al. Sequential nephron blockade versus sequential renin-angiotensin system blockade in resistant hypertension: A prospective, randomized, open blinded endpoint study. *J Hypertens* 2012; 30(8): 1656–1664.
27. MacKay JH, Arcuri KE, Goldberg AI et al. Losartan and low-dose hydrochlorothiazide in patients with essential hypertension. A double-blind, placebo-controlled trial of concomitant administration compared with individual components. *Arch Intern Med* 1996; 156(3): 278–285.
28. Roush GC, Holford TR, Guddati AK. Chlorthalidone compared with hydrochlorothiazide in reducing cardiovascular events: Systematic review and network meta-analyses. *Hypertension* 2012; 59(6): 1110–1117.
29. Peterzan MA, Hardy R, Chaturvedi N, Hughes AD. Meta-analysis of dose-response relationships for hydrochlorothiazide, chlorthalidone, and bendroflumethiazide on blood pressure, serum potassium, and urate. *Hypertension* 2012; 59(6): 1104–1109.
30. Patel A, Group AC, MacMahon S et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): A randomised controlled trial. *Lancet* 2007; 370(9590): 829–840.
31. Mogensen CE, Viberti G, Halimi S et al. Effect of low-dose perindopril/indapamide on albuminuria in diabetes: Preterax in albuminuria regression: PREMIER. *Hypertension* 2003; 41(5): 1063–1071.
32. Sica D, Bakris GL, White WB et al. Blood pressure-lowering efficacy of the fixed-dose combination of azilsartan medoxomil and chlorthalidone: A factorial study. *J Clin Hypertens (Greenwich)* 2012; 14(5): 284–292.
33. Bakris GL, Sica D, White WB et al. Antihypertensive efficacy of hydrochlorothiazide vs chlorthalidone combined with azilsartan medoxomil. *Am J Med* 2012; 125(12): 1229 e1221–1229 e1210.
34. Cushman WC, Bakris GL, White WB et al. Azilsartan medoxomil plus chlorthalidone reduces blood pressure more effectively than olmesartan plus hydrochlorothiazide in stage 2 systolic hypertension. *Hypertension* 2012; 60(2): 310–318.
35. Makani H, Bangalore S, Romero J et al. Peripheral edema associated with calcium channel blockers: Incidence and withdrawal rate—a meta-analysis of randomized trials. *J Hypertens* 2011; 29(7): 1270–1280.
36. de la Sierra A. Mitigation of calcium channel blocker-related oedema in hypertension by antagonists of the renin-angiotensin system. *J Hum Hypertens* 2009; 23(8): 503–511.
37. Jamerson K, Weber MA, Bakris GL et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008; 359(23): 2417–2428.

38. Bakris GL, Sarafidis PA, Weir MR et al. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): A prespecified secondary analysis of a randomised controlled trial. *Lancet* 2010; 375(9721): 1173–1181.
39. Dahlof B, Sever PS, Poulter NR et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): A multicentre randomised controlled trial. *Lancet* 2005; 366(9489): 895–906.
40. Pepine CJ, Handberg EM, Cooper-DeHoff RM et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): A randomized controlled trial. *JAMA* 2003; 290(21): 2805–2816.
41. Ogihara T, Saruta T, Rakugi H et al. Combinations of olmesartan and a calcium channel blocker or a diuretic in elderly hypertensive patients: A randomized, controlled trial. *J Hypertens* 2014; 32(10): 2054–2063; discussion 2063.
42. Matsuzaki M, Ogihara T, Umemoto S et al. Prevention of cardiovascular events with calcium channel blocker-based combination therapies in patients with hypertension: A randomized controlled trial. *J Hypertens* 2011; 29(8): 1649–1659.
43. Umemoto S, Ogihara T, Matsuzaki M et al. Effects of calcium channel blocker benidipine-based combination therapy on target blood pressure control and cardiovascular outcome: A sub-analysis of the COPE trial. *Hypertens Res* 2017; 40(4): 376–384.
44. Stergiou GS, Makris T, Papavasiliou M et al. Comparison of antihypertensive effects of an angiotensin-converting enzyme inhibitor, a calcium antagonist and a diuretic in patients with hypertension not controlled by angiotensin receptor blocker monotherapy. *J Hypertens* 2005; 23(4): 883–889.
45. Mann JF, Anderson C, Gao P et al. Dual inhibition of the renin-angiotensin system in high-risk diabetes and risk for stroke and other outcomes: Results of the ONTARGET trial. *J Hypertens* 2013; 31(2): 414–421.
46. Basile J, Neutel J. Overcoming clinical inertia to achieve blood pressure goals: The role of fixed-dose combination therapy. *Ther Adv Cardiovasc Dis* 2010; 4(2): 119–127.
47. Lanier G, Sankholkar K, Aronow WS. Azilsartan, aliskiren, and combination antihypertensives utilizing renin-angiotensin-aldosterone system antagonists. *Am J Ther* 2014; 21(5): 419–435.
48. Oparil S, Melino M, Lee J et al. Triple therapy with olmesartan medoxomil, amlodipine besylate, and hydrochlorothiazide in adult patients with hypertension: The TRINITY multicenter, randomized, double-blind, 12-week, parallel-group study. *Clin Ther* 2010; 32(7): 1252–1269.
49. Lacourciere Y, Taddei S, Konis G et al. Clinic and ambulatory blood pressure lowering effect of aliskiren/amlodipine/hydrochlorothiazide combination in patients with moderate-to-severe hypertension: A randomized active-controlled trial. *J Hypertens* 2012; 30(10): 2047–2055.
50. Toth K, PIANIST Investigators. Antihypertensive efficacy of triple combination perindopril/indapamide plus amlodipine in high-risk hypertensives: Results of the PIANIST study (Perindopril-Indapamide plus Amlodipine in high risk hypertensive patients). *Am J Cardiovasc Drugs* 2014; 14(2): 137–145.
51. Calhoun DA, Lacourciere Y, Chiang YT, Glazer RD. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: A randomized clinical trial. *Hypertension* 2009; 54(1): 32–39.
52. Brown MJ, McInnes GT, Papst CC et al. Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): A randomised, parallel-group trial. *Lancet* 2011; 377(9762): 312–320.
53. Weir MR, Hsueh WA, Nesbitt SD et al. A titrate-to-goal study of switching patients uncontrolled on antihypertensive monotherapy to fixed-dose combinations of amlodipine and olmesartan medoxomil +/- hydrochlorothiazide. *J Clin Hypertens (Greenwich)* 2011; 13(6): 404–412.
54. Volpe M, de la Sierra A, Kreutz R et al. ARB-based single-pill platform to guide a practical therapeutic approach to hypertensive patients. *High Blood Press Cardiovasc Prev* 2014; 21(2): 137–147.
55. Chow CK, Thakkar J, Bennett A et al. Quarter-dose quadruple combination therapy for initial treatment of hypertension: Placebo-controlled, crossover, randomised trial and systematic review. *Lancet* 2017; 389(10073): 1035–1042.
56. Bennett A, Chow CK, Chou M et al. Efficacy and safety of quarter-dose blood pressure-lowering agents: A systematic review and meta-analysis of randomized controlled trials. *Hypertension* 2017; 70(1): 85–93.
57. Kjeldsen SE, Messerli FH, Chiang CE et al. Are fixed-dose combination antihypertensives suitable as first-line therapy? *Curr Med Res Opin* 2012; 28(10): 1685–1697.



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*Louis Hofstetter and Franz H. Messerli*

## INTRODUCTION

The term 'essential hypertension' was coined by Frank (1) more than a century ago, stating 'Because in this disease the increase in tone of the small arteries in the whole body (which leads to an increase in blood pressure) is the primary event...I will, in the following, name this disease, essential hypertension (essentielle Hypertonie)'. The concept of hypertension being essential (i.e. serving to force blood through sclerotic arteries to the target organs) remained alive and well into the 1970s. Authoritative statements like 'For aught we know, the hypertension might be a compensatory mechanism that should not be tampered with even were it certain that we could control it' (2) and 'May not the elevation of blood pressure be a natural response to guarantee a more normal circulation to the heart, brain and kidneys' (3) reinforced clinicians' fear that blood pressure (BP) could be lowered too much in susceptible patients. The reluctance of many physicians to expose their patients to antihypertensive therapy is therefore not surprising, because abrupt lowering of BP in hypertensive emergencies, paradoxically, can increase target organ disease such as renal failure, encephalopathy and coronary ischemia and even directly cause heart attacks, stroke and death (4). Over time, however, the pendulum began to swing toward the other extreme, and the dictum, 'the lower the better', became the leitmotiv for many doctors treating hypertension. The extensive, thorough meta-analysis of Lewington et al. (5) corroborated and amplified this concept by stating that 'usual BP is strongly and directly related to vascular (and overall) mortality without any evidence of a threshold down to at least 115/75 mmHg'. Such statements threatened to put an end to the 'essentiality' of essential hypertension. Thus, the optimal BP targets recommended by national and international guidelines committees have shifted downward over the last years and decades.

## THE J-CURVE CONCEPT

Aggressive BP-lowering notwithstanding, a concept that never quite vanished from the published reports and surfaced in many randomised trials was the J-curve

phenomenon, describing an increase in cardiovascular events with lower blood pressure. Obviously, such a J-curve exists, because a BP of 0 encompasses a 100% mortality.

Three decades ago, Cruickshank et al. reported in patients with coronary artery disease (CAD) a J-shaped relationship between risk of death from myocardial infarction (MI) and diastolic blood pressure (DBP) (6). The nadir of the J-curve in DBP was at 85–90 mmHg, with an increase of mortality from MI on either side of this range. However, no such J-curve was found in patients without CAD or for systolic blood pressure.

Seven years later, such a J-curve was also reported in patients with evidence of left ventricular hypertrophy. In the Skaraborg Hypertension Project Lindblad et al. (7) found an increased risk for a first MI when lowering DBP in hypertensive men with ischaemic/hypertrophic ECG. Not surprisingly, the opposite was true in men with a normal ECG. In 484 elderly men taking antihypertensive medication over a 10-year follow-up, Merlo et al. (8) found the risk of an ischaemic cardiac events in patients with DBP  $\leq$  90 mmHg and taking antihypertensive medication to be 4 times higher and remained significantly high after adjusting for other cardiovascular risk factors.

However, recently, several large randomised trials showed that even low BP targets may reduce cardiovascular events and mortality. This brings up the question whether there is a J-curve within a 'physiologic' range of BP.

## CORONARY ARTERY PERFUSION

Blood flow regulation of the coronary circulation is different from that of cerebral and renal circulation. Because the coronary arteries are perfused predominantly during diastole, such a J-curve, if existing within a physiologic range, would most probably emerge in coronary events due to low DBP. The coronary vascular bed is unique because during systole, the contracting left ventricular (LV) myocardium compresses intramyocardial vessels and obstructs its own blood flow. Coronary perfusion pressure is determined by the pressure gradient between the aorta and the right atrium in diastole. This is in contrast to cerebral perfusion, which occurs in systole and diastole.



Normal epicardial coronary arteries are conductance vessels and do not offer much resistance to blood flow. They branch into a series of arterioles in which a substantial pressure drop occurs, then arborizing into a dense capillary network, which in diastole produces a 'suction' wave. This capillary density is reduced in the presence of left ventricular hypertrophy (9).

Autoregulation, the ability to maintain systemic perfusion pressures over a wide pressure range, is present in coronary, renal and cerebral blood flow (10). Such autoregulatory mechanisms result from vascular myogenic response to blood pressure fluctuations, intrinsic production of vasoactive substances in response to metabolic demands, and remote controlling mechanisms (11). For instance, cerebral blood flow remains constant over the range of arterial pressures from approximately 60–150 mmHg (12). In the coronary circulation, these autoregulatory mechanisms can also compensate for the various degrees of proximal epicardial coronary obstruction. However, in individuals with restrictions of coronary perfusion, e.g. secondary to stenosis of epicardial coronary arteries, an excessive fall in DBP compromises oxygen supply of myocytes when perfusion pressure distal to a stenosis falls below a critical level at which autoregulation is effective. This results in a vicious cycle with myocardial ischemia, elevated LV filling pressures, which in turn further reduces the perfusion gradient, resulting in progressive deterioration of cardiac function, and finally multiorgan failure.

Microvascular disease, occasionally a result of long-standing hypertension, and increased cardiac oxygen requirement states can result in relative ischemia, too. SBP is a major determinant of cardiac afterload, and consequently of myocardial energy requirements. In the presence of left ventricular hypertrophy, there is increased metabolic demand but compromised delivery of oxygen and nutrients during systole and diastole.

## LARGE OBSERVATIONAL STUDIES REPORTING A J-CURVE

In the INVEST (International Verapamil-Trandolapril Study) trial in 22,576 patients with hypertension and CAD, after adjustment for baseline heart failure, a J-shaped relationship with DBP was observed for the primary outcome (all-cause death, nonfatal MI or nonfatal stroke) with a nadir estimated at 116/83 mmHg (Figure 42.1). Not surprisingly, revascularised patients tolerated a significantly lower DBP than nonrevascularised patients (13).

Similarly, in 22,672 patients of the CLARIFY (Prospective Observational Longitudinal Registry of Patients with Stable Coronary Artery Disease) registry after a median follow-up of 5 years, SBP of less than 120 mmHg, or DBP of less than 70 mmHg were associated with an increased risk for the primary outcome (composite of cardiovascular death, myocardial infarction, or stroke) (hazard ratio [HR] 1.56, 95% confidence interval [CI] 1.36–1.81, adjusted HR 1.41, 95% CI 1.24–1.61, respectively) after extensive adjustment (14).

In the same year, McEvoy et al. (15) reported a similar J-curve in the ARIC (Atherosclerosis in Communities) patient population of 11,565 individuals with low DBP associated with subsequent coronary heart disease and mortality over a median follow-up of 21 years. Compared to DBP 80–89 mmHg, patients with a DBP <60 mmHg showed the highest relative hazard for incident CAD (HR 1.49, 95% CI 1.2–1.85,  $p < 0.001$ ) and death (HR 1.32, 95% CI 1.13–1.55,  $p < 0.001$ ), all adjusted for multiple risk factors. In a subcomponent analysis, this association seemed stronger for fatal CAD, respectively, MI compared to revascularisation (HR 1.88, 95% CI 1.01–3.49,  $p = 0.046$ , HR 1.6, 95% CI 1.19–2.14,  $p = 0.002$ ). No such association between DBP and stroke was found after adjusting for clinical confounders, in particular for SBP. When stratifying

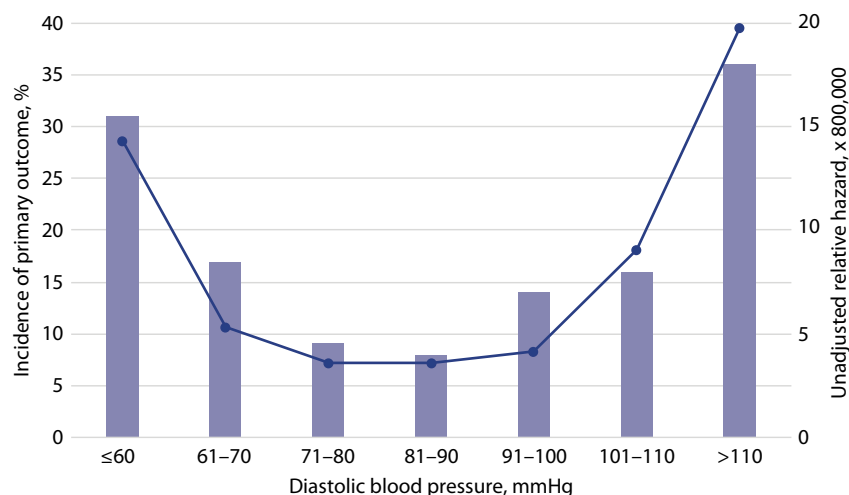


**Figure 42.1** Relationships between different achieved levels of diastolic blood pressure and the incidence of the primary outcome (first occurrence of all-cause death, nonfatal myocardial infarction, or nonfatal stroke) (column), expressed as percentage and unadjusted relative hazard (line) in the International Verapamil-Trandolapril Study trial (INVEST). (Adapted from Messerli FH et al. *Ann Intern Med.* 2006; 144(12): 884–893.)

their study sample by SBP, McEvoy et al. found an excess risk among those with SBP  $\geq 120$  mmHg, which is a pulse pressure  $>60$  mmHg, which in turn is a marker for advanced disease of the vascular tree (15). Among patients with a DBP  $<60$  mmHg, elevated levels of highly sensitive cardiac troponin-T were more prevalent compared to a DBP of 80–89 mmHg, suggesting ongoing and chronic subclinical myocardial damage.

In line with these results, in 10,001 patients with CAD of the Treating to New Targets (TNT) Trial over a follow-up of 4.9 years, a time-dependent, nonlinear, multivariate Cox proportional hazard model identified a nadir of 146.3/81.4 mmHg where the event rate for a composite of death from coronary disease, nonfatal MI, resuscitated cardiac arrest, and fatal or nonfatal stroke was lowest (16).

## RANDOMISED CONTROLLED TRIALS AND THE J-CURVE

In 18,790 patients with hypertension of the HOT (Hypertension Optimal Treatment) trial, designed to determine whether different DBP targets led to different rates of major cardiovascular events (MI, stroke, cardiovascular death), the lowest incidence of major cardiovascular events occurred at a mean achieved DBP of 82.6 mmHg, and the lowest risk of cardiovascular mortality occurred at 86.5 mmHg. In high-risk patients with evidence of coronary ischemia, there was an 22% increase in the risk of MI when the DBP was  $<80$  mmHg compared with  $<85$  mmHg (17).

In the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial, there is a trend to an increased incidence in MI with a nadir of DBP at 79 mmHg for patients without, and 76 mmHg for patients with CAD. However, this interaction did not attain statistical significance. Of note, there was an increase in the ratio of MI to stroke with lower DBP, indicating target organ heterogeneity in that the optimal on-treatment DBP for cerebroprotection seems to be below that for cardioprotection (18).

In a recent post hoc analyses of two randomised trials (19), ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial ACE-inhibitors) and TRANSCEND (Telmisartan Randomised Assessment Study of ACE Intolerant), a mean DBP  $\leq 70$  mmHg in 5352 patients was associated with a greater risk of the composite primary outcome (cardiovascular death, MI, stroke, and hospital admission for heart failure) (HR 1.31, 95% CI 1.20–1.42), MI (1.55, 1.33–1.80), hospital admission for heart failure (1.59, 1.36–1.86) and all-cause death (1.16, 1.06–1.28) compared to the 14,305 patients with a DBP 70–80 mmHg. A pretreatment and mean on-treatment DBP of about 75 mmHg was associated with the lowest risk. In the 4052 patients with a SBP less than 120 mmHg on treatment, the risk of the composite cardiovascular outcome (adjusted HR 1.14, 95% CI 1.03–1.26), cardiovascular death (1.29, 1.12–1.49), and all-cause death (1.28, 1.15–1.42) were significantly increased compared to the 16,099 patients in whom SBP was 120–140 mmHg during treatment. Interestingly, mean achieved SBP more accurately predicted outcomes than baseline or time-updated SBP, and was associated with the lowest risk at approximately 130 mmHg, and at 110–120 mmHg

risk increased for the combined outcome, cardiovascular death, and all-cause death except stroke.

In contrast, in the 9361 patients of SPRINT (Systolic Blood Pressure Intervention Trial), the HR for a composite outcome of MI, acute coronary syndrome not resulting in MI, stroke, acute decompensated heart failure or death from cardiovascular causes with intensive treatment (mean SBP 121.5 mmHg over follow-up) was 0.75 (95% CI, 0.64–0.89;  $p < 0.001$ ) compared to the standard-treatment arm with a mean SBP of 134.6 mmHg (20). Even among the 2510 patients older than 75 years, intensive treatment resulted in an HR for the composite outcome of 0.66 (95% CI 0.51–0.85) compared to standard treatment. However, these benefits came at the cost of an increase in secondary chronic kidney disease (HR 3.14, 95% CI 1.66–6.37,  $p < 0.001$ ) and blood pressure measurement in SPRINT was unique and cannot be compared with other studies (21). Interestingly, when looking at baseline DBP, a post hoc analysis showed a U-shaped association with the hazard of the primary outcome, but the effects of intensive SBP intervention on the primary outcome was not influenced by baseline DBP level ( $p$  for interaction 0.83) (22).

## J-CURVE IN CEREBROVASCULAR DISEASE

If low DBP were simply a marker of poor vascular health, and not *eo ipso* responsible for adverse outcomes, low DBP would independently be associated with cerebrovascular events, too. However, this association is less robust. In the 6287 subjects of the Rotterdam Study, a J-shaped relation was found between both systolic and diastolic blood pressure and the incidence of stroke. For DBP, the increase of the risk in the lowest category (DBP  $<65$  mmHg) compared with the reference was statistically significant (23). In the 4736 patients of the SHEP (the Systolic Hypertension in the Elderly Program) study, the benefit of treatment with a calcium channel blocker or diuretic disappeared in patients who developed diastolic hypotension (DBP  $<70$  mmHg), and DBP  $<55$  mmHg was associated with a higher risk of ischaemic cardiac events, but also with stroke (24). In the 20,330 patients aged  $\geq 50$  years of the PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial, the risk for first recurrence of stroke of any type was higher in the group with SBP  $<120$  mmHg (adjusted HR 1.29; 95% CI 1.07–1.56) compared to SBP  $>140$  mmHg (25).

This is in contrast to data from the PROGRESS (Perindopril Protection Against Recurrent Stroke) study, where the association of stroke incidence with achieved follow-up SBP level was strong and continuous with no evidence of a J-curve in the range from 112–168 mmHg. A similar pattern was found for DBP levels from 72–102 mmHg. Furthermore, no such J-curve for stroke was found in a post hoc analysis of INVEST (13). And in the recent Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial in 4733 diabetic patients randomised to conventional or intensive SBP lowering treatment, the HR for fatal and nonfatal stroke in those assigned to an intensive systolic BP lowering (mean achieved BP of 119.3/64.4 mmHg) was 0.59 (95% CI 0.39–0.89,  $p = 0.001$ ) compared to those randomised to conventional treatment (mean achieved BP 133.5/70.5 mmHg). These conflicting results can be explained by the point-of-no-return hypothesis with

regard to BP management. In the REGARDS (Reasons for Geographic and Racial Differences in Stroke) cohort, (26) during 6.3 years of follow-up, individuals taking three antihypertensive drugs and a systolic BP below 120 mmHg were at a higher risk for stroke (HR 2.48 [1.63–3.77]) than those with SBP <120 on no antihypertensive medications.

## J-CURVE IN THE ELDERLY POPULATION

Such a point of no return might play its role in the elderly population, too. In the PARTAGE (Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population) study, in 1127 nursing home residents older than 80 years, a significant interaction for all-cause mortality in propensity-score-matched subsets was found between low SBP and treatment with two or more BP-lowering agents (adjusted HR 2.05, 95% CI 1.37–2.48,  $p < 0.001$ ) (27). Their hypertension may not always have been well controlled and have resulted in vascular damage. Thus, hypertensive target organ disease and alterations in the vascular tree were no longer amenable to regression, and further BP lowering resulted in adverse events. In contrast, among the 2636 community-dwelling participants of SPRINT elderly (mean age 79.9 years, 37.9% women), there was a 33% relative risk reduction for all-cause mortality in the intensive treatment arm (21) (Table 42.1).

## J-CURVE IN HEART FAILURE

In 1049 patients with acute heart failure requiring hospitalisation, there was an inverse linear relationship between SBP at admission and mortality over a follow-up of 18 months. In patients with LVEF  $\leq 40\%$ , every 10-mmHg decrease in SBP was associated with a 16% increase in mortality (28). On the other hand, in patients with HFpEF, the relationship was nonlinear, resulting in a J-shaped curve. In another cohort of 56,942 patients aged 79.7 years (SD 22.8) admitted for acute heart failure, higher DBP levels were associated with lower 30-day and 1-year mortality rates in unadjusted analysis that persisted after adjustment for baseline characteristics and SBP values (29).

In 2584 patients with heart failure with reduced ejection fraction (HFrEF, LVEF  $\leq 40\%$ ), Lee et al. (30) reported a J-curve association between mortality and on-treatment BP with a nadir at 136.0/76.6 mmHg. Low BP is frequently encountered in HFrEF and it is associated with poor outcomes. This brings up the question whether there is an optimal BP level for dosing neurohormonal blockers or whether one should uptitrate to the maximal tolerable dose. In post hoc analysis of randomised controlled trials, such medication still showed benefit in patients with low BP. In the COPENICUS (Carvedilol Prospective Randomized Cumulative Survival) trial, although patients with the lowest SBP were at the highest risk of an event, they experienced the greatest absolute benefit from treatment with carvedilol (31). In the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) trial, baseline SBP and DBP did not modify the effect of candesartan on all-cause mortality (32). In PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor-Neprilysin

Inhibitor] with ACEI [Angiotensin-Converting Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, all-cause mortality rates were highest in patients with the lowest SBP (33). However, these patients had the same benefits over enalapril as patients with higher baseline SBP (HR for the primary endpoint 0.88 (0.74–1.06) in patients with baseline SBP <110 mmHg and 0.81 (0.65–1.02) in those with a SBP >140 mmHg ( $p$  for interaction = 0.55).

In 1130 patients with heart failure with preserved ejection fraction (HFpEF, LVEF  $\geq 50\%$ ), Lee et al. (30) found a J-curve for mortality with a nadir of 127.9/72.7 mmHg. In 1802 propensity-matched patients with HFpEF and a SBP at discharge of <120 vs.  $\geq 120$  mmHg, the hazard ratio for all-cause mortality was significantly higher for SBP <120 mmHg at 30 days (HR 2.07, 95% CI 1.45–2.95;  $p < 0.001$ ), at 1 year (HR 1.36, 95% CI 1.16–1.59;  $p < 0.001$ ), and at 6 years (HR 1.17, 95% CI 1.05–1.30;  $p = 0.005$ ) with a J-shaped curve in the restricted cubic spline plot of the 3906 prematched patients (34). Importantly, current guidelines, recommending lowering BP in heart failure patients as low as in hypertensive patients without heart failure, are based on evidence that management of hypertension lowers incident heart failure, but not on evidence that lowering BP improves outcome of heart failure patients (21,35) (Figure 42.2). Reverse causality might be the underlying mechanism; low blood pressure may simply be an epiphenomenon of impaired cardiac function. Similar phenomena have been described for other heart failure risk factors such as obesity, cholesterol or smoking (36–38).

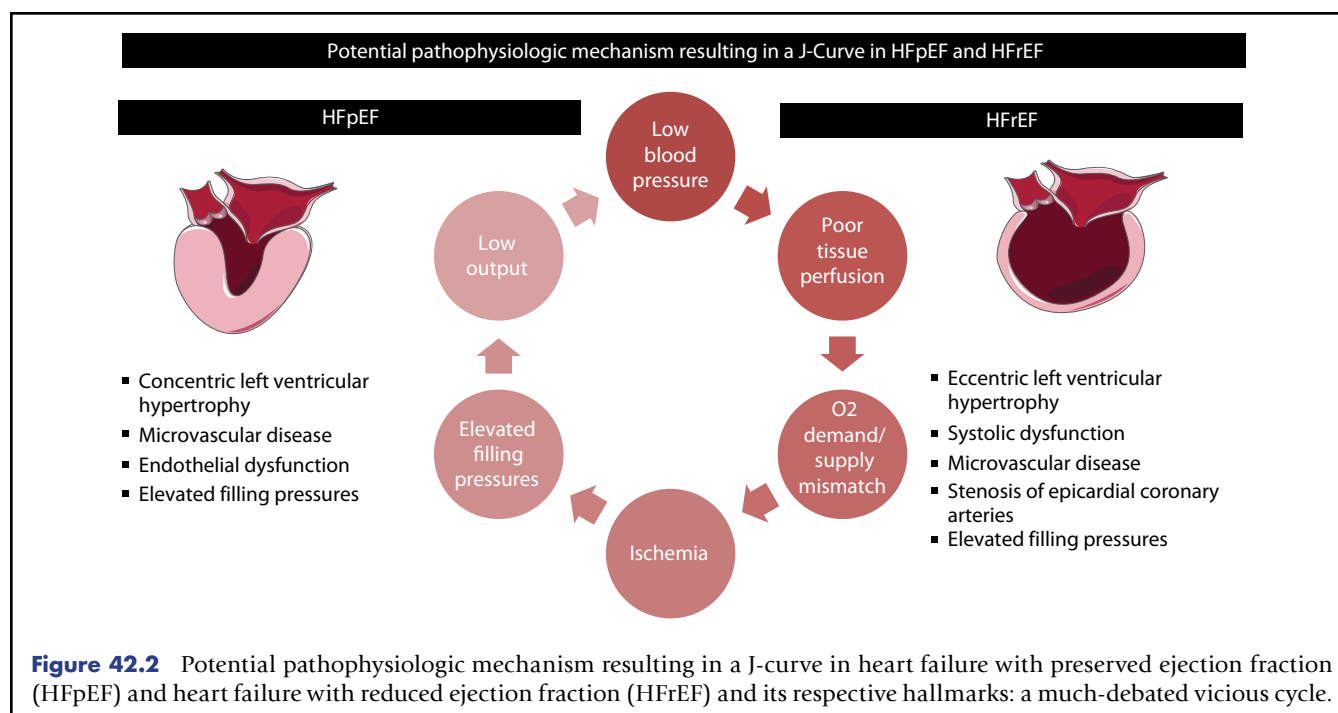
## REVERSE CAUSALITY

1. *Chronic illness.* Several pathophysiologic mechanisms have been proposed to explain the existence of a J-curve. The J-curve with increased mortality with low blood pressure could be an epiphenomenon related to underlying chronic illness, being a mere marker of this illness thereby increasing mortality (39). In a meta-analysis of 40,233 hypertensive patients from seven randomised trials, a positive J-curve relationship between DBP as well as SBP and both fatal cardiovascular and noncardiovascular mortality was found. The authors concluded that the J-curve relationship is possibly attributed to poor health, because it was independent of either treatment or type of events (40). This paradoxical association with lower BP and increased mortality has sometimes also been explained in terms of patient frailty. The highest drop in BP can be found in individuals who are most at risk of adverse outcomes because of underlying illness over follow-up. In a UK cohort with 144,403 patients  $\geq 80$  years of age registered with family practices, Ravindrarajah et al. (41) showed an accelerated decline of SBP in the last 2 years of life. They showed that elderly patients with SBP <120 mmHg did have higher risks of mortality than those with SBP of 120–139 mmHg, independent of frailty. The pattern of accelerated decline was identical in patients on and off antihypertensive medication, with the relative odds of SBP <120 mmHg in the last 3 months of life than 5 years previously in treated (odds ratio

**Table 42.1** Summary of selected clinical studies reporting association between blood pressure and adverse endpoints

| First author/study name | Year | Patients (n) | Mean age (yrs) | Mean entry SBP (mmHg) | Mean entry DBP (mmHg) | Includes patients with CVD | Mean follow-up (years) | MI  | Stroke    | Total mortality     | J-Point mmHg                                                                    |
|-------------------------|------|--------------|----------------|-----------------------|-----------------------|----------------------------|------------------------|-----|-----------|---------------------|---------------------------------------------------------------------------------|
| ACCORD-BP (52)          | 2010 | 4733         | 62.2           | 139                   | 76                    | Yes                        | 4.7                    | –   | No        | –                   | –                                                                               |
| ARIC (15)               | 2016 | 11,565       | 56.7           | 121                   | 73                    | Yes                        | 21                     | Yes | No        | Yes                 | DBP <60                                                                         |
| CLARIFY (14)            | 2016 | 22,672       | 65.2           | 133.7                 | 78.2                  | Yes                        | 5 (median)             | Yes | No        | Yes                 | SBP 120 /DBP 70                                                                 |
| Cruickshank (6)         | 1987 | 2145         | 55             | na                    | 109                   | Yes                        | 6.1                    | Yes | No        | No                  | DBP 85–90 (in ischaemic patients only), SBP in patients >=60 years 137–148 mmHg |
| Fagard (50)             | 2007 | 4695         | 70             | 173                   | 85                    | Yes                        | 1–8                    | Yes | Yes       | Yes                 | DBP 70–75 in patients with CAD                                                  |
| Hansson (51)            | 1998 | 18,790       | 62             | 170                   | 105                   | Yes                        | 3.8                    | Yes | Yes (SBP) | No (cardiovascular) | SBP 138.8 mmHg, DBP 86.5 mmHg                                                   |
| IPPPSH (47)             | 1985 | 6357         | 52             | na                    | 108                   | No                         | 4.0                    | Yes | –         | –                   | DBP 92                                                                          |
| Kannel (44)             | 2004 | 7798         | 35–80          | na                    | –                     | No                         | 10                     | Yes | Yes       | No                  | DBP 80–89                                                                       |
| Lee (30)                | 2017 | 5625         | 68             | 131                   | 78                    | Yes                        | 2.2                    | –   | –         | Yes                 | SBP 132.4<br>DBP 74.2                                                           |
| Lindblad (7)            | 1994 | 2574         | 59             | 157                   | 92                    | Yes                        | 7.4                    | Yes | –         | –                   | DBP 90–95                                                                       |
| ONTARGET/TRANSCEND (19) | 2008 | 30,937       | 66.5           | 142                   | 82                    | Yes                        | 4.6 (median)           | Yes | No        | Yes                 | SBP 120<br>DBP 70                                                               |
| PARTAGE (27)            | 2012 | 1127         | 88.5           | 138                   | 73                    | Yes                        | 2                      | –   | –         | –                   | –                                                                               |
| Pepine (49)             | 2003 | 22576        | 66             | 149                   | 86                    | Yes                        | 2.7                    | Yes | Yes       | Yes                 | DBP 76.4–85.8                                                                   |
| SPRINT (22)             | 2016 | 9361         | 67.9           | 140                   | 78                    | Yes                        | 3.3 (median)           | Yes | No        | Yes                 | –                                                                               |
| Stewart (46)            | 1979 | 169          | 44             | na                    | 124                   | No                         | 6.3                    | Yes | –         | –                   | DBP 100–109                                                                     |
| TNT (16)                | 2010 | 10,001       | 61             | 131                   | 78                    | Yes                        | 5.5                    | Yes | Yes (DBP) | Yes                 | SBP 146.3, DBP 81.4                                                             |
| VALUE (18)              | 2016 | 15,244       | 67             | 150                   | 86                    | Yes                        | 4.2                    | Yes | No        | –                   | SBP 128, DBP 75                                                                 |
| Wilhelmsen (48)         | 1987 | 6569         | 40–60          | na                    | 107                   | No                         | 3.9                    | Yes | Yes       | Yes                 | DBP 86–89                                                                       |

Abbreviations: Na, not available; SBP, systolic blood pressure; DBP, diastolic blood pressure.



[OR] 6.06, 95% CI 5.4–6.81) and untreated patients (OR 6.31, 95% CI 5.3–7.52).

2. *Heart failure.* Low blood pressure may be an epiphenomenon of impaired cardiac function (42), even though previous studies have controlled for left ventricular function (16,43). However, only randomisation can ensure that comparison of groups is similar with respect to the underlying risk.
3. *Increased pulse pressure.* Last but not least, the J-curve might be an epiphenomenon of increased arterial stiffness, marking advanced vascular disease and thereby increasing mortality (44). Pulse pressure is an independent risk factor for CAD irrespective of SBP. In a pooled analysis of individual patient data from three large trials involving approximately 8000 patients, a 10 mmHg wider pulse pressure increased the risk of major cardiovascular complications ( $p < 0.001$ ). At any given level of SBP, the risk also increased with lower DBP ( $p = 0.001$ ) (45). Therefore, low DBP might simply be a surrogate for poor vascular health. There seems to be an inverse relationship between DBP and CAD (i.e. the lower the DBP the greater the risk of CAD), but such is not the case with cerebrovascular disease. In the aforementioned INVEST trial, there was a significant and progressive preponderance of MI over strokes at low DBP (13). Moreover, in the sensitivity analysis of the TNT trial, the J-curve phenomenon for DBP, but also SBP persisted after controlling for pulse pressure (16).

### J-CURVE IN THE ERA OF REVASCULARISATION

In the INVEST trial, revascularisation interacted with the relationship between DBP and the risk for the primary

outcome only as DBP decreased, suggesting that patients who had revascularisation before enrolment tolerated lower DBP relatively better than those who did not have revascularisation (13). However, the data are not unequivocal. In the CLARIFY cohort, no significant effect modification was found with previous revascularisation and the primary outcome (14). In the TNT trial (16), a significant interaction between SBP with prior bypass surgery was found ( $p$  interaction 0.004) with higher event rates at low SBP after bypass surgery; however, reverse causality cannot be excluded.

### CONCLUSION

A large body of evidence shows that there is a J-curve in hypertension. The J-shaped curve seems particularly prominent in CAD, and less so in cerebrovascular disease. However, to conclusively document its pathogenesis, prospective properly randomised controlled trials are needed.

### REFERENCES

1. Frank E. *Deutsches archiv fur klin. Medizin.* 1911; 103: 397–412.
2. White P. *Heart Disease.* 1st ed. McMillan, New York, NY; 1931.
3. Tice F. *Practice of Medicine.* 1st ed. WFPC, Hagerstown, MD; 1924.
4. Grossman E, Messerli FH, Grodzicki T, Kowey P. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? *JAMA* 1996; 276(16): 1328–1331.
5. Lewington S, Clarke R, Qizilbash N et al., Prospective Studies C. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360(9349): 1903–1913.
6. Cruickshank JM, Thorp JM, Zacharias FJ. Benefits and potential harm of lowering high blood pressure. *Lancet* 1987; 1(8533): 581–584.
7. Lindblad U, Rastam L, Ryden L et al. Control of blood pressure and risk of first acute myocardial infarction: Skaraborg Hypertension Project. *BMJ* 1994; 308(6930): 681–686.



8. Merlo J, Ranstam J, Liedholm H et al. Incidence of myocardial infarction in elderly men being treated with antihypertensive drugs: Population based cohort study. *BMJ* 1996; 313(7055): 457–461.
9. Harrison DG, Barnes DH, Hiratzka LF et al. The effect of cardiac hypertrophy on the coronary collateral circulation. *Circulation* 1985; 71(6): 1135–1145.
10. Pijls NHJ DBB. *Coronary Pressure*. Kluwer Academic Publishers, Dordrecht; 1997.
11. Tzeng YC, Ainslie PN. Blood pressure regulation IX: Cerebral autoregulation under blood pressure challenges. *Eur J Appl Physiol* 2014; 114(3): 545–559.
12. Lassen NA. Cerebral blood flow and oxygen consumption in man. *Physiol Rev* 1959; 39(2): 183–238.
13. Messerli FH, Mancia G, Conti CR et al. Dogma disputed: Can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006; 144(12):884–893.
14. Vidal-Petiot E, Ford I, Greenlaw N et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: An international cohort study. *Lancet* 2016; 388(10056): 2142–2152.
15. McEvoy JW, Chen Y, Rawlings A et al. Diastolic blood pressure, subclinical myocardial damage, and cardiac events: Implications for blood pressure control. *J Am Coll Cardiol* 2016; 68(16): 1713–1722.
16. Bangalore S, Messerli FH, Wun CC et al. J-curve revisited: An analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial. *Eur Heart J* 2010; 31(23): 2897–2908.
17. Cruickshank JM. Antihypertensive treatment and the J-curve. *Cardiovasc Drugs Ther* 2000; 14(4): 373–379.
18. Kjeldsen SE, Berge E, Bangalore S et al. No evidence for a J-shaped curve in treated hypertensive patients with increased cardiovascular risk: The VALUE trial. *Blood Press* 2016; 25(2): 83–92.
19. Bohm M, Schumacher H, Teo KK et al. Achieved blood pressure and cardiovascular outcomes in high-risk patients: Results from ONTARGET and TRANSCEND trials. *Lancet* 2017; 389(10085): 2226–2237.
20. Group SR, Wright JT, Jr., Williamson JD et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med* 2015; 373(22): 2103–2116.
21. Williamson JD, Supiano MA, Applegate WB et al. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged  $\geq 75$  Years: A Randomized Clinical Trial. *JAMA* 2016; 315(24): 2673–2682.
22. Beddhu S, Chertow GM, Cheung AK et al. Influence of baseline diastolic blood pressure on effects of intensive compared to standard blood pressure control. *Circulation* 2017.
23. Voko Z, Bots ML, Hofman A et al. J-shaped relation between blood pressure and stroke in treated hypertensives. *Hypertension* 1999; 34(6): 1181–1185.
24. Curb JD, Pressel SL, Cutler JA et al. Effect of diuretic-based anti-hypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. *JAMA* 1996; 276(23): 1886–1892.
25. Ovbiagele B, Diener HC, Yusuf S et al. Level of systolic blood pressure within the normal range and risk of recurrent stroke. *JAMA* 2011; 306(19): 2137–2144.
26. Howard G, Banach M, Cushman M et al. Is blood pressure control for stroke prevention the correct goal? The lost opportunity of preventing hypertension. *Stroke* 2015; 46(6): 1595–1600.
27. Benetos A, Labat C, Rossignol P et al. Treatment With Multiple Blood Pressure Medications, Achieved Blood Pressure, and Mortality in Older Nursing Home Residents: The PARTAGE Study. *JAMA Intern Med* 2015; 175(6): 989–995.
28. Nunez J, Nunez E, Fonarow GC et al. Differential prognostic effect of systolic blood pressure on mortality according to left-ventricular function in patients with acute heart failure. *Eur J Heart Fail* 2010; 12(1): 38–44.
29. Vidan MT, Bueno H, Wang Y et al. The relationship between systolic blood pressure on admission and mortality in older patients with heart failure. *Eur J Heart Fail* 2010; 12(2): 148–155.
30. Lee SE, Lee HY, Cho HJ et al. Reverse J-curve relationship between on-treatment blood pressure and mortality in patients with heart failure. *JACC Heart Fail* 2017; 5(11): 810–819.
31. Rouleau JL, Roecker EB, Tendera M et al. Influence of pretreatment systolic blood pressure on the effect of carvedilol in patients with severe chronic heart failure: The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. *J Am Coll Cardiol* 2004; 43(8): 1423–1429.
32. Meredith PA, Ostergren J, Anand I et al. Clinical outcomes according to baseline blood pressure in patients with a low ejection fraction in the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) Program. *J Am Coll Cardiol* 2008; 52(24): 2000–2007.
33. Bohm M, Young R, Jhund PS et al. Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: Results from PARADIGM-HF. *Eur Heart J* 2017; 38(15): 1132–1143.
34. Tsimploulis A, Lam PH, Arundel C et al. Systolic blood pressure and outcomes in patients with heart failure with preserved ejection fraction. *JAMA Cardiol* 2018.
35. Messerli FH, Rimoldi SF, Bangalore S. The transition from hypertension to heart failure: Contemporary update. *JACC Heart Fail* 2017; 5(8): 543–551.
36. Khalid U, Ather S, Bavishi C et al. Pre-morbid body mass index and mortality after incident heart failure: The ARIC Study. *J Am Coll Cardiol* 2014; 64(25): 2743–2749.
37. Fonarow GC, Abraham WT, Albert NM et al. A smoker's paradox in patients hospitalized for heart failure: Findings from OPTIMIZE-HF. *Eur Heart J* 2008; 29(16): 1983–1991.
38. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. *J Am Coll Cardiol* 2004; 43(8): 1439–1444.
39. Boshuizen HC, Izaks GJ, van Buuren S, Ligthart GJ. Blood pressure and mortality in elderly people aged 85 and older: Community based study. *BMJ* 1998; 316(7147): 1780–1784.
40. Boutitie F, Gueyffier F, Pocock S et al. Interventional IPSCIDAOA. J-shaped relationship between blood pressure and mortality in hypertensive patients: New insights from a meta-analysis of individual-patient data. *Ann Intern Med* 2002; 136(6): 438–448.
41. Ravindrarajah R, Hazra NC, Hamada S et al. Systolic blood pressure trajectory, frailty, and all-cause mortality  $>80$  years of age: Cohort study using electronic health records. *Circulation* 2017; 135(24): 2357–2368.
42. Tuomilehto J, Ryyanen OP, Koistinen A et al. Low diastolic blood pressure and mortality in a population-based cohort of 16913 hypertensive patients in North Karelia, Finland. *J Hypertens* 1998; 16(9): 1235–1242.
43. Protogerou AD, Safar ME, Iaria P et al. Diastolic blood pressure and mortality in the elderly with cardiovascular disease. *Hypertension* 2007; 50(1): 172–180.
44. Kannel WB, Wilson PW, Nam BH et al. A likely explanation for the J-curve of blood pressure cardiovascular risk. *Am J Cardiol* 2004; 94(3): 380–384.
45. Blacher J, Staessen JA, Girerd X et al. Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. *Arch Intern Med* 2000; 160(8): 1085–1089.
46. Stewart IM. Relation of reduction in pressure to first myocardial infarction in patients receiving treatment for severe hypertension. *Lancet* 1979; 1(8121): 861–865.
47. Myocardial infarctions and cerebrovascular accidents in relation to blood pressure control. The IPPPSH collaborative group. *J Hypertens Suppl* 1985; 3(3): S513–S518.
48. Wilhelmsen L, Berglund G, Elmfeldt D et al. Beta-blockers versus diuretics in hypertensive men: Main results from the HAPPHY trial. *J Hypertens* 1987; 5(5): 561–572.
49. Pepine CJ, Handberg EM, Cooper-DeHoff RM et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): A randomized controlled trial. *JAMA* 2003; 290(21): 2805–2816.
50. Fagard RH, Staessen JA, Thijs L et al. On-treatment diastolic blood pressure and prognosis in systolic hypertension. *Arch Intern Med* 2007; 167(17): 1884–1891.
51. Hansson L, Zanchetti A, Carruthers SG et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998; 351(9118): 1755–1762.
52. Group AS, Cushman WC, Evans GW et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; 362(17): 1575–1585.



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# A POLYPILL FOR GLOBAL CARDIOVASCULAR PREVENTION: CURRENT DATA AND FUTURE PERSPECTIVES

# 43

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## INTRODUCTION

The concept of a cardiovascular (CV) polypill is more than 15 years old. It was originally proposed in 2001 by a World Health Organization and Wellcome Trust expert group (1) which thought that the combination in a single tablet of four drugs, each with a documented ability to prevent CV disease (a beta-blocker, an ACE inhibitor, a statin and aspirin) might reduce the risk of future events in patients with previous CV disease (2). This was taken up 2 years later by Wald and Law (3), who claimed that a polypill containing six agents with proven or potential CV prevention ability (three antihypertensive drugs, a statin, aspirin and folic acid) would reduce the incidence of CV events by more than 80% in individuals older than 55 years, thereby implementing, if extensively adopted, primary and secondary CV prevention to an unprecedented degree. However, this 'vaccination approach' found strong opposition from the scientific community which thought that, besides being unproven, the extent of CV prevention claimed by Wald and Law (3) was unrealistic. Concern was also generated by the unknown consequences of medicalizing the entire population, the inconveniences and costs of potential adverse reactions to the high number of assumed drugs, the untoward psychological effects of lifetime treatment in healthy individuals and, last but not least, the possibility of favouring, via the belief of living in a drug-protected state, unhealthy life habits. Without suitable clinical studies demonstrating its efficacy, the polypill strategy did not go beyond an attractive hypothesis and was abandoned.

Based on Wald and Law's initial idea, various authors proposed a more selective use of the polypill for primary prevention in individuals without CVD but at high CV risk (4). There is no definitive proof of the efficacy, safety or cost-effectiveness of this approach, although its feasibility has been shown in several pilot studies (5,6). Overall, the studies show that the use of a CV polypill significantly increases treatment adherence (7,8). None of these studies had the power to detect differences in the rate of new coronary events. Therefore, the results of new studies, some currently underway, are required to confirm that the polypill can play a role in the primary prevention of coronary disease.

In the last few years a large body of evidence has been obtained that adherence to antihypertensive, lipid lowering, antidiabetic and other drugs that improve CV risk profile is so low as to make low adherence perhaps the most important factor opposing CV risk factor control in the general population (9–16). It has also been found that complex treatments, such as those based on multiple daily pills, adversely affect adherence, which can be considerably improved by treatment simplification (17–21). The fact that treatment simplification is the main characteristic of a polypill has revived this strategy as a means to improve the notoriously low efficacy of primary and secondary CV prevention at the population level (22–26).

This chapter reviews the arguments provided by epidemiology and treatment in favour of a polypill-based approach to CV prevention, the evidence that this approach is effective in CV protection, the advantages and inconveniences that may be associated with the lumping of several drugs in a single tablet and the challenges and opportunities for a global implementation of a polypill strategy either in low income and developed countries.

## RATIONALE FOR USE OF THE POLYPILL IN THE ERA OF PERSONALIZED AND PRECISION MEDICINE

The worldwide epidemic of CV disease sparked the concept of a CV polypill nearly 15 years ago. It seems counterintuitive that in the time of personalized medicine, a CV polypill would be deemed one of the most scalable strategies to contain the atherosclerotic CV disease pandemic (27). However, the rise of CV risk factors, especially in low- and middle-income countries (LMIC), where accessibility to preventive CV therapy is scarce, imposes the need for scalable, simple, cost-effective strategies to ensure adequate therapeutic treatment to prevent first or recurrent CV events.

The CV pandemia of the twenty-first century shows remarkable parallels with the global human immunodeficiency virus (HIV) infection scenario of the 1990s. The antiretroviral polypill was proposed at the turn of the millennium as a public health strategy to contain a

communicable disease which affected patients all over the world, especially in LMICs, with very low accessibility to effective antiretroviral treatment, at a time where antiretroviral therapy effectively led to the chronification of the disease. Two decades later, the antiretroviral polypill has effectively controlled the HIV pandemic based on three simple benefits: accessibility, adherence and cost-effectiveness. The current CV landscape calls for a similar strategy to contain what has become the leading cause of death worldwide, responsible for over 17 million deaths worldwide in 2011 and expected to reach 24 million deaths by 2030. The sanitary, social and economic costs of this reality call for simple solutions to contain this grave burden. The CV polypill represents one of these strategies, which should be included within an integrated public health approach to promote healthy lifestyles, correct CV risk factors and effectively implement CV therapies in high-risk patients.

### THERAPEUTIC ADHERENCE: PREVALENCE AND CLINICAL IMPACT

Medication nonadherence, defined as a patient's passive failure to follow a prescribed drug regimen, remains a significant concern for healthcare professionals and patients. Medication adherence represent a person's behaviour, and it depends on multiple factors related to the patient, the health system, the disease, the treatment and socioeconomic factors (Figure 43.1).

On average, one-third to one-half of patients do not comply with prescribed treatment regimens (28). In a meta-analysis of 20 observational studies involving 376,162 patients, a summary estimate of the prevalence of poor adherence across multiple drug classes as measured by pharmacy refill data was 43% (12). The World Health Organization has reported similar figures of adherence both to CV and non-CV medications (29). In secondary prevention, adherence to medication has been reported to be below the 50% mark 6 months following the CV event (30), but alarmingly even in the immediate aftermath of acute cardiac events adherence is suboptimal. In a population cohort of 4591 post-myocardial infarction (MI)

patients, 18% did not fill their cardiac medications even once in the 4 months after discharge from hospital (31). These percentages represent summary estimates, and there are substantial differences in adherences to specific CV medications, even among those prescribed for the same CV condition.

### CLINICAL IMPACT OF MEDICATION NONADHERENCE

Lack of adherence has been associated with an increase in long-term CV events, including acute MI (AMI), stroke, CV mortality, and all-cause mortality (32,33). In a meta-analysis conducted with data from the European Union, lack of adherence was identified as the cause of 13 CVD deaths per 100,000 inhabitants, and 9% of all CVD deaths were attributed to nonadherence. Good adherence is associated with a 20% lower risk of CVD and a 35% reduction in all-cause mortality (12). In a recent study of 90,869 Medicare beneficiaries who had prescriptions for ACE inhibitors/ARBs, beta-blockers and statins, after AMI hospitalization, adherence was measured by proportion of days covered during 180 days following hospital discharge. The authors used proportional hazards models to estimate hazard ratios of mortality for groups adherent to two, one, or none of the therapies versus group adherent to all three therapies. Only a striking 49% of the patients adhered (PDC >80%) to all three therapies. Compared with being adherent to all three therapies, multivariable-adjusted hazard ratios for mortality were 1.65 (95% CI: 1.54–1.76) for being nonadherent (PDC <80%) to all three therapies (34). In another study carried out by Bansilal et al. that included patients who had experienced an AMI or had atherosclerosis and were treated with statins and ACE inhibitors, AMI patients with full adherence had 27% fewer events compared to their nonadherent counterparts, and 19% fewer events than patients with partial adherence. In patients with atherosclerosis, a 44% reduction in events was observed compared to nonadherent patients, and a 24% reduction compared to partially adherent patients. In terms of costs, lack of adherence

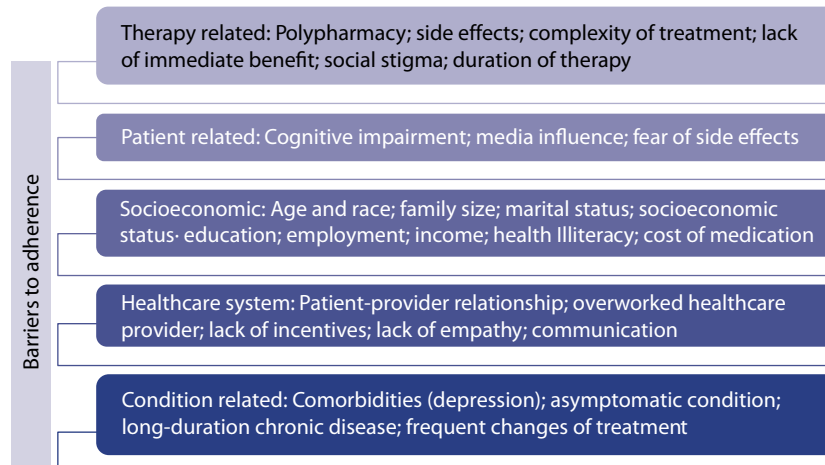


**Figure 43.1** The multifactorial nature of nonadherence to medications.

is associated with a long-term increment of \$907/year/patient (33). Finally, a recent Swedish nationwide cohort study of 601,527 users of low-dose aspirin for primary or secondary prevention showed that patients who discontinued aspirin had a higher rate of CV events than those who continued (multivariable-adjusted hazard ratio, 1.37; 95% CI, 1.34–1.41), corresponding to an additional CV event observed per year in 1 of every 74 patients who discontinued aspirin (35). Data from meta-analysis cohort registries or prospective cohort studies consistently shows the overwhelming clinical impact (and economic burden) of medication nonadherence in major adverse events, most of which are preventable on the basis of following the prescribed treatment regimen.

Based on the results of the studies measuring the impact of the polypill on adherence and risk factor control, the recent guidelines have included the polypill as one of the most effective strategies to improve adherence. This has been the case of the 2016 European Guidelines on CV disease prevention (36), as well as the recently published 2017 ST elevation MI guidelines (37). Recently, the Spanish consensus document on the clinical use of the polypill issued a series of recommendations related to adherence. Major recommendations included establishing good doctor-patient communication and relationships, agreeing on the therapeutic plan with the patient to improve their commitment and involvement, simplifying the therapeutic regimen, periodically assessing therapeutic adherence and implementing adherence reinforcement strategies over time (38). Similarly, the Chilean Society of Cardiology, the Argentine Society of Cardiology and the Argentine Federation of Cardiology recommended the use of polypills to increase adherence (39).

### **EVIDENCE OF THE CLINICAL USE OF A CARDIOVASCULAR POLYPILL: ACCESSIBILITY, ADHERENCE, RISK FACTOR CONTROL, COST-EFFECTIVENESS AND PATIENT PREFERENCE**

The low adherence to prescribed CVD drugs and the impact on secondary prevention has prompted investigators to evaluate strategies for improvement. Such strategies can be implemented through the development of government health policies and interventions in routine clinical practice. One of these strategies is treatment simplification, as it can be assumed that any strategy aimed at simplifying treatment, such as the polypill, will result in improved adherence.

The recently published 2017 Cochrane systematic review synthesized the evidence on the use of the polypill and included 13 polypill trials (9059 participants) done in 32 countries that investigated the effect of different combinations compared with usual care, placebo, or active comparator that had been published up to 2016 (40).

Polypill trials have been designed as phase 2 studies to investigate pharmacodynamics and short-term and medium-term safety of the polypills (41). These trials were not powered to detect differences in clinical outcomes (Table 43.1). The rationale for use of a phase 2 design has been largely based on the understanding that the components of polypills have been widely accepted, approved,

and used for primary and secondary prevention of atherosclerosis. Two large prospective, randomized clinical trials are underway to assess the benefit on outcomes of the use of a polypill in primary prevention, the HOPE-4 study, (NCT01826019) as well as in secondary prevention, the SECURE (Secondary prEvention of CardiovasCUlar disease in the Elderly trial), a European collaborative project funded by the EU Framework Programme for Research and Innovation, Horizon 2020 (NCT02596126).

### **ACCESSIBILITY**

Nearly 80% of all CV deaths take place in LMICs, where access to medication is dismal (reports from the PURE studies show 8–14% accessibility to antiplatelets, statins and antihypertensive medication in secondary prevention with figures dropping to the low single digits in rural areas) (42).

### **ADHERENCE**

The polypill has been consistently shown in clinical trials including different populations to be the single most efficient (and certainly scalable) strategy to significantly improve adherence. Four trials reported the effect of polypills on adherence, which was 44% higher in the polypill group than in the comparator group ( $p < 0.001$ ) (8,43–45). Interestingly, participants with low baseline adherence were more likely to show improvements in adherence with polypills than were participants with high baseline adherence levels. This finding supports the position that polypills can be used to reduce inequities that manifest in lower baseline medication adherence rates in disadvantaged populations (46).

### **RISK FACTOR CONTROL**

Thirteen trials (7638 participants) reported the effect on systolic blood pressure, which was 6.3 mmHg lower in the polypill group than in the comparator group ( $p < 0.001$ ). Eleven trials (6565 participants) reported the effect on total cholesterol, which was 0.6 mmol/L lower in the polypill group ( $p < 0.001$ ) (41). Because most trials that included risk factor changes had short-term follow-up, the differences seen between the polypill and comparator groups were not maintained long enough to manifest differences in clinical event rates.

### **COST-EFFECTIVENESS**

At the health system level, although increasing drug use increases short-term costs, it leads in the long term to a decrease in the number of significant CV events and costs associated with hospitalization and treatment of the event. The net result is a reduction in healthcare costs. A systematic review found that adherence greater than 80% is associated with a reduction in expenditure of up to 18% (47). A mathematical model applied to the economic consequences of the lack of adherence in chronic diseases showed that long-term adherence reduces costs of medical



| <b>Table 43.1</b> Clinical trials using a cardiovascular polypill for primary and secondary CV prevention                                                |                                                                                                                                                                                                       |                                                                                                                                                                                            |                                                                                                             |                                               |
|----------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| <b>Trial/Sample size/Principal investigator(s)</b>                                                                                                       | <b>Population</b>                                                                                                                                                                                     | <b>Polypill composition</b>                                                                                                                                                                | <b>Outcomes</b>                                                                                             | <b>Status</b>                                 |
| <i>Primary prevention</i>                                                                                                                                |                                                                                                                                                                                                       |                                                                                                                                                                                            |                                                                                                             |                                               |
| Indian Polycap Study (TIPS)<br>n = 2053<br>Yusuf S, Pais P                                                                                               | Men and women aged 40–80 y without CVD and with at least 1 CV risk factor in India                                                                                                                    | Aspirin 100 mg, simvastatin 20 mg, ramipril 5 mg, hydrochlorothiazide 12.5 mg, atenolol 50 mg                                                                                              | Feasibility; effect on risk factor levels; safety and tolerability                                          | Completed                                     |
| Poly-Iran: Phase II Study of Heart Polypill Safety and Efficacy in Primary Prevention of CV Disease<br>n = 475<br>Marshall T, Malekzadeh R, Malekzadeh F | Men and women aged 50–80 y without indications or contraindications for aspirin, BP-lowering drugs, and statins in Iran                                                                               | Aspirin 81 mg, hydrochlorothiazide 12.5 mg, endapril 2.5 mg, atorvastatin 20 mg                                                                                                            | Effect on risk factor levels; safety and tolerability                                                       | Completed                                     |
| Combination Therapy Trial<br>n = 200<br>Furberg C, Mendis S, Soliman EZ                                                                                  | Age >40 y without CVD and with estimated 10-y total CVD risk score >20% in Sri Lanka                                                                                                                  | Aspirin 75 mg, simvastatin 10 mg, lisinopril 10 mg, hydrochlorothiazide 10 mg (Red Heart Pill 2b)                                                                                          | Effect on estimated 10-y total CVD risk score                                                               | Completed                                     |
| IMProving Adherence using combination therapy (IMPACT)<br>n = 497<br>Rodgers A, Selak A                                                                  | Established CVD or 5-year risk $\geq 15\%$                                                                                                                                                            | Aspirin 75 mg, simvastatin 40 mg, and lisinopril 10 mg with either atenolol 50 mg or hydrochlorothiazide 12.5 mg                                                                           | Effect on Adherence to recommended drugs and mean change in blood pressure and LDL-cholesterol at 12 months | Completed                                     |
| Indian Polycap Trial (TIPS)-3<br>n = 5000<br>Yusuf S, Pais P, Xavier D, Liu L                                                                            | Primary prevention with estimated yearly CVD event rate of >1% using the INTERHEART risk score in China and India                                                                                     | Polycap; dose to be chosen after completion of the TIPS-K trials                                                                                                                           | Major CVD events; neurocognitive function                                                                   | Estimated study completion date: January 2019 |
| Heart Outcomes Prevention Evaluation (HOPE)-3<br>N = 12,500<br>Yusuf S, Lonn E                                                                           | Primary prevention in men aged >55 y and women aged >65 y with at least 1 CV risk factor and women aged >60 y with at least 2 risk factors and with average BP and cholesterol levels in 22 countries | Rosuvastatin 10 mg, candesartan 16 mg/hydrochlorothiazide 12.5 mg (2 × 2 factorial design)                                                                                                 | Major CVD events; neurocognitive function; renal function                                                   | Completed                                     |
| <i>Secondary prevention</i>                                                                                                                              |                                                                                                                                                                                                       |                                                                                                                                                                                            |                                                                                                             |                                               |
| FOCUS Trial in Secondary Prevention<br>Phase 1: n = 2000, Phase 2: n = 800<br>Fuster V                                                                   | Survivors of myocardial infarction in Spain and Latin American countries                                                                                                                              | Aspirin 100 mg, simvastatin 40 mg, ramipril 2.5, 5, 10 mg (Trinomia)                                                                                                                       | Adherence; feasibility; effect on risk factor levels; safety and tolerability                               | Completed                                     |
| Use of a Multidrug Pill in Reducing CV Events (n = 2000/<br>Thom SA, Rodgers A                                                                           | Established CVD or high-risk primary prevention (5-y CVD risk of >15%) in India, Netherlands, UK                                                                                                      | Aspirin 75 mg, atenolol 50 mg, simvastatin 40 mg, lisinopril 10 mg (RedHeart pill 1) or aspirin 75 mg, hydrochlorothiazide 12.5 mg, simvastatin 40 mg, lisinopril 10 mg (Red Heart pill 2) | Adherence; effect on risk factor levels; safety and tolerability; CVD events (secondary outcome)            | Completed                                     |
| SECURE<br>Secondary Prevention<br>N = 3206<br>Fuster V<br>Castellano JM                                                                                  | Post MI over 65 years old<br>Spain, France, Italy, Germany, Poland, Czech Republic, Hungary                                                                                                           | Aspirin 100 mg, atorvastatin 20 or 40 mg, ramipril 2.5, 5, 10 mg (Trinomia)                                                                                                                | Composite MACE: revascularization, CV death, ischaemic stroke, recurrent MI                                 | Estimated study completion date: May 2020     |

care by reducing hospitalizations and admissions to the emergency room, despite the increased pharmaceutical expenditure (48). Various pharmaco-economic models have been published comparing the use of a polypill strategy versus usual care. The polypill has been shown to be cost-effective even in the most adverse models due to its effect on clinical outcomes based on improved adherence, and risk factor control (49,50).

## PATIENT PREFERENCE

Various trials of polypills versus usual care have reported data on acceptability of the polypill concept to physicians or patients, or both, participating in these trials (46). Although subject to social desirability bias (whereby participants might report favourably to be seen in a better light), the overwhelming response was favourable towards use of a polypill in routine clinical practice. Further additional studies surveyed patients and physicians who were not involved in clinical trials with similar positive response to the polypill concept. The most commonly mentioned advantages were the ease and convenience of taking pills, cost-saving benefits and improved safety from simplifying, and therefore decreasing confusion about, pill regimens.

## CLINICAL USE OF THE POLYPILL

### POLYPILLS FOR PRIMARY PREVENTION

The clinical indication of a polypill is largely determined by the specific composition of the available polypills. Currently, the Fuster polypill (which includes aspirin 100 mg, atorvastatin 20 or 40 mg, and ramipril 2.5, 5 or 10 mg), is first-in-class and has been approved for commercialization in more than 50 countries. In this current scenario, treatment with the polypill could be indicated in primary prevention patients with a high or very high CV risk (determined by risk charts, presence of diabetes or subclinical vascular disease, including carotid atheroma plaques, low ankle-brachial pressure index or chronic renal failure, high calcium score, or presence of abdominal aortic aneurysm) and low risk of bleeding with ASA in diabetic patients older than 50 years with at least one associated CV risk factor including smoking, hypertension, dyslipidemia, low LDL-C or microalbuminuria. This rationale is based on the HOPE study (51), which showed a benefit in the primary prevention of diabetic patients treated with ramipril, and also on recommendations from clinical guidelines on the management of diabetic patients (52), and in diabetic patients older than 50 years with chronic renal disease and macroalbuminuria or microalbuminuria. The data are based on various studies that demonstrate the renal protection of the renin-angiotensin system (RAS) blockers in primary prevention in diabetic patients (53,54), and on some clinical guidelines recommendations on the management of diabetic patients (54,55). Finally, the polypill may be used in patients with high CV risk and clinical or subclinical ventricular dysfunction, in whom ramipril would be prescribed for the cardiac pathology (56), and statin and aspirin for the high CV risk.

The HOPE-3 study explored the role of three drugs, the RAS angiotensin-receptor blocker (ARB) candesartan, the thiazide diuretic hydrochlorothiazide (HCTZ), and a 10-mg dose of rosuvastatin into one pill. HOPE-3 enrolled more than 12,000 people from around the world, including men over age 55 years and women over age 65 years with at least one risk factor for heart disease. The study had a  $2 \times 2$  factorial design. In the first arm of the study (57), participants were randomly assigned to receive placebo or a low dose of a candesartan/hydrochlorothiazide combination. Then, in the second arm (58), they were again randomly assigned to receive rosuvastatin 10 mg or placebo. Investigators analysed the blood pressure changes, then the cholesterol changes, and finally blood pressure and cholesterol levels in those who received both treatments versus placebo (59).

In HOPE-3's first arm (57), those who received BP-lowering treatment consisting of candesartan 16 mg/day and hydrochlorothiazide 12.5 mg/day did not have significantly fewer occurrences of a composite of CV-related death, nonfatal MI, or nonfatal stroke (the first co-primary outcome) a mean of 5.6 years later compared with those who received placebo (4.1% vs. 4.4%, respectively). The second co-primary outcome, which added heart failure, cardiac arrest or revascularization to the composite, was also not significantly different between the groups (4.9% vs. 5.2%). However, prespecified subgroup analysis, which divided baseline systolic BP into thirds, showed that the participants with upper-third measurements ( $>143.5$  mmHg) receiving candesartan/hydrochlorothiazide did meet the co-primary outcomes.

In the second arm (58), the participants who were randomized to rosuvastatin 10 mg/day also met both primary outcomes versus placebo ( $p = 0.002$  and  $p < 0.001$  for both group comparisons, respectively) and had a 24% lower risk for CV events.

The trial's third arm (59) assessed patients randomized to rosuvastatin plus candesartan/hydrochlorothiazide versus rosuvastatin plus placebo versus candesartan/hydrochlorothiazide plus placebo versus two placebos. The findings showed that those who received both of the treatment drugs together had significantly lower rates of the first primary outcome versus the double-placebo group (3.6% vs. 5.0%, respectively,  $p = 0.005$ ), as well as the second primary outcome (4.3% vs. 5.9%,  $p = 0.003$ ).

The results of this trial indicate that the use of low-dose statin therapy with rosuvastatin 10 mg is superior to placebo in reducing long-term CV events in an intermediate-risk population (CV event rate  $\sim 1\%$ /year). On the other hand, a fixed-dose combination of candesartan 16 mg + HCTZ 12.5 mg daily was not superior to placebo in reducing CV events despite a 6-mmHg decrease in SBP and a 3-mmHg decrease in DBP. There was effect modification by baseline SBP such that patients who truly had hypertension (i.e. SBP  $>143.5$  mmHg) appeared to benefit with combination treatment. A fixed-dose combination of all three drugs appeared to have CV benefits that were mostly similar to those observed with rosuvastatin compared with placebo. In the subset of patients  $\geq 70$  years, there was no signal of differential cognitive decline with all three strategies compared with placebo.

Many features of this trial deserve comment. First, it was designed as a practical trial, with few mandatory visits to titrate medications based on cholesterol or BP response. This might thus lend itself well to a 'polypill' approach for large populations but lowering of LDL-C and/or BP

could have been greater if these were periodically assessed and dosages adjusted accordingly, particularly for the BP-lowering arm. Second, rather than enrolling patients based on baseline values of LDL-C or BP, they were enrolled based on their baseline risk for CV events. This has been endorsed by the most recent lipid guidelines and was also recently observed in the SPRINT trial for BP lowering. These results thus provide further validation of the 2015 lipid guidelines approach. Next, the trial enrolled patients from many different countries, with close to 50% of Asian ethnicity. Since these countries have a progressively larger burden of CVD, these results may be more broadly generalizable. For the BP arm, it is unclear if the use of other agents such as chlorthalidone or amlodipine would have demonstrated a benefit rather than HCTZ/candesartan.

## POLYPILLS FOR SECONDARY PREVENTION

The polypill has been predominantly investigated in the context of secondary CV prevention, particularly in patients with a previous MI, for a number of reasons. First, in patients with established CV disease the efficacy of drug-related correction of several CV factors (antiplatelet, BP-lowering and lipid-lowering treatments) has been unequivocally proven by randomized trials (60–62), and a greater protective ability has usually been documented when these drugs are used in combination (63). Two, compared to primary prevention, secondary prevention is characterized by a more favourable NNT ratio; that is, by a greater number of hospitalizations and events saved for a given number of treated patients, with thus a more favourable cost-benefit ratio, at least over a midtime treatment duration. Finally, despite its high economic burden for the healthcare system, in patients with CV disease control of CV risk factors is still largely ineffective (64) due to under-prescription of a number of drugs with documented protective effects, low treatment compliance and, in developing countries, limited availability of medicaments and unaffordable treatment costs.

In the last 10 years, several studies have shown that the polypill strategy can favourably affect CV prevention in patients with established CV disease. The second Indian Polycap Study (TIPS-2) (6) made use of ramipril, atenolol, hydrochlorothiazide, simvastatin and aspirin (supplemented by potassium) in a single capsule (half-dose of the drugs) and compared its effects to the administration of two capsules (full doses of the drugs) for 8 weeks in more than 500 patients with CV disease or type 2 diabetes. Compared to one capsule, two Polycap capsules significantly reduced BP by a further 2.8/1.7 mmHg, total serum cholesterol by 7.2 mg/dL and LDL-cholesterol by 6.6 mg/dL, with a calculated reduction in the relative risk of coronary disease of 69% and stroke of 57%. Discontinuation of treatment was low and similar in the two groups (6.9% and 7.8%, respectively) showing that the Polycap had a good tolerability.

The use of a multidrug pill in reducing CV events (UMPIRE) trial (44) has assessed whether a polypill strategy lowered BP and serum cholesterol in several thousand patients with established or at high risk (>15% over 5 years) of developing CV disease, the primary goal being to determine whether this might be associated with an improved adherence to treatment. Two polypill types were used, depending on the extent of baseline comorbidities: a polypill containing aspirin, simvastatin, atenolol and

lisinopril and another containing aspirin, simvastatin, lisinopril and hydrochlorothiazide. Over a median follow-up of 15 months, the polypill group exhibited a significant improvement in adherence to treatment than the usual care group (86% vs. 65%,  $p < 0.01$ ), an even larger improvement occurring in patients with lower adherence to treatment at baseline. The improved adherence was accompanied by a significantly greater reduction of systolic BP (−2.6 mmHg) and LDL-cholesterol (−4.2 mg/dL) while no significant differences in serious adverse or CV events between groups were observed.

The Improving Adherence using Combination Therapy (IMPACT) trial (43) randomized more than 500 patients with established CV disease or a high CV risk (>15% risk of an event over 5 years) to usual care (free combinations) or two different polypill strategies (aspirin, simvastatin, lisinopril and atenolol or hydrochlorothiazide) according to an open-label study design and with self-measured adherence as the primary endpoint. BP and cholesterol reductions were non-significantly different between the two treatment groups and so were serious adverse and CV events. This was not the case for adherence, however, which after 12 months from randomization was 46% and 81% in the usual and polypill treatment strategy, respectively, the difference being statistically significant ( $p < 0.001$ ). Similar observations were made in the Kanyini Guidelines Adherence with Polypill (Kanyini GAP) open-label trial (45) in which more than 600 patients with a risk profile and a polypill composition similar to those of the UMPIRE trial showed, after one-and-a-half years from initial randomization to treatment, a much greater adherence to the polypill-based strategy than to the usual free combination care (70% vs. 47%,  $p < 0.0001$ ). This was unexpectedly not accompanied by a greater BP and serum cholesterol reduction, a finding possibly accounted for by the more limited power of the study compared to that provided by the much higher number of patients available for the UMPIRE trial.

Further interesting evidence has more recently been obtained by research conducted in Spain from the Centro Nacional de Investigaciones Cardiovasculares (CNIC) in collaboration with Ferrer International. The Fuster polypill, containing aspirin (100 mg), simvastatin (40 mg) and ramipril at various doses (2.5, 5 or 10 mg) was extensively tested in preclinical and clinical studies to document a similar efficacy with the free association of its individual components (65,66). It was thereafter tested in a randomized study on about 700 patients with a history of MI (8). Compared to a 9 months separate administration of the three drugs, the polypill group showed similar effects on BP (on-treatment systolic value 129.6 vs. 128.6 mmHg), serum LCD-cholesterol (89.9 vs. 91.7 mg/dL), serious adverse events (23% vs. 21%) and death (0.3% in either group). In line with other studies, however, adherence to treatment as measured by both self-reported questionnaire and by pill counting was significantly better in the polypill than in the group in which drugs were given separately, the difference amounting to 22% (50.8% vs. 41.0%,  $p = 0.019$ ). Similar findings have been obtained with a second polypill also containing aspirin and ramipril at various doses, but replacing simvastatin with atorvastatin 20 mg, with the addition of the information provided by careful in vitro and in vivo studies which have shown the safety, tolerability and bioequivalence of all its components with the drugs given separately (67). This has led this polypill to receive in 2014 the approval of the

**Table 43.2** Clinical situations in which a preferential use of the polypill in secondary prevention of cardiovascular disease is recommended

- Patients not adherent to one or more components of the best drug therapy established for secondary CV prevention (aspirin, ACEi or ARB, statin) or who have factors predicting poor adherence
- Patients with blood pressure or LDL-cholesterol not at target with equivalent doses of the drugs and with suspected low adherence
- Patients well controlled with the individual drugs (substitution strategy)
- Patients with several comorbidities needing additional drugs to those included in the polypill

Abbreviations: ARB, angiotensin receptor blocker; ACEi, angiotensin converting enzyme inhibitor.

European Medical Agency for use in secondary prevention of CV events in adult patients. The indication specifically mentions that use should consist of substitution therapy whenever patients are adequately controlled by the polypill components at equivalent doses. Based on all these data, the European Society of Hypertension recently published a position statement on the clinical use of the polypill (68). Table 43.2 shows the clinical situations in which use of the polypill may be considered.

## POTENTIAL INCONVENIENCES

The polypill approach is not exempted by potential inconveniences whose impact can in some instances be minimized while in other instances may be not entirely avoidable. From a technical standpoint, the decision to include different compounds in a polypill must consider a number of problems; that is, the chemical compatibility, physical stability and pharmacokinetic properties of each component versus the others (69,70). Combining components with different solubility and sensitivity to heat and moisture, for example, can reduce the availability of some drugs as well as, in part, their pharmacokinetic and pharmacodynamics characteristics (67). Large differences in the concentration of some drugs versus others, for example, a few milligrams of one compound versus hundreds of another, may also modify the expected overall biological effect. Even if the original pharmacological characteristics of the drugs are retained, care should always be taken to only combine drugs with complementary mechanisms and a similar duration of action to ensure a balanced effect throughout the between-dose interval. The problems may of course increase steeply as the number of drugs in a polypill increases.

Clinical inconveniences must also be taken into consideration. Although minimized by the availability of polypills with different doses of drug components, use of fixed-dose combinations is characterized by a reduced flexibility of the titration process by which a physician tries to reach optimal risk factor control, such as when the dose of statin to achieve the LDL-cholesterol target needs to be increased whereas no increase of antihypertensive drugs is needed because target BP values have already been achieved, or vice-versa. Another problem may be that contraindication to one polypill component prevents use of the whole polypill, and the appearance of serious side effects to one component of the polypill may also mean

discontinuation of the entire polypill, leaving the patient unprotected against all risk factors before treatment is resumed on a free basis. This may not be avoidable by switching to polypills with lower doses of the drug because some drug-related side effects (cough by ACE inhibitors, myalgia by statins, occult bleeding by aspirin, etc.) may occur also at low doses (71). A similar problem can also materialize, albeit to a lesser degree, when patients miss a polypill dose, an event that in real life remains common even when adherence improves. Finally, based on recent data, there is still some concern on whether privileging CV risk factor correction by a comprehensive simple pharmacological approach might minimize, in the eye of the patient, the importance to pursue this goal by appropriate lifestyle changes as well. This can be avoided, however, by implementing patient's information and education.

## GLOBAL IMPLEMENTATION OF A POLYPILL STRATEGY: CHALLENGES AND OPPORTUNITIES

The current landscape of CV morbidity and mortality, together with the projections of the devastating effects especially in LMICs, calls for an urgent reconciliation with the polypill concept of all stakeholders in order to overcome the critical barriers that prevent the implementation of a major public health action item for the global CVD community. The public health implications of polypill use are potentially substantial, especially in low-resource settings but also in all settings where adherence to secondary prevention is low. The large treatment gaps in secondary prevention, especially in LMICs, are well documented. Despite the demonstrated benefits of effective and inexpensive drug therapy for secondary prevention of recurrent CV events, these therapies are underused in many LMICs where the greatest burden of CV disease occurs. The grave burden of noncommunicable diseases has not escalated in the health agenda of various policy makers precisely because of the chronicity of these diseases. There needs to be a conceptual adaptation to the reality of noncommunicable diseases by all stakeholders (societal, patients' associations, policy makers, scientific associations, industry and insurers) to adopt and implement simple, cost-effective scalable strategies – the so-called best-buy public health interventions, such as the CV polypill for secondary prevention. The CV polypill, used as an important component of a comprehensive public health approach for secondary prevention and high-risk primary prevention, is a vital strategy for treatment expansion. The future prospects for the widespread use of the polypill as a crucial public health intervention will depend on key strategies to address the clinical, regulatory and systemic barriers.

## SUMMARY AND CONCLUSIONS

In 2011, for the first time in the history of mankind, noncommunicable diseases became the leading cause of death worldwide. The change in trend is obviously multifactorial and very complex, as it is the paradoxical result of social, economic and health system growth worldwide. Vaccination and infectious disease control, changing



dietary habits worldwide, sedentary behaviour, globalization, industrialization resulting in a shift from manual to sedentary labour, tobacco and sugary beverage surge in LMICs and rapid urbanization all have played a role in this epidemic transition.

At the same time, the increase in CV risk factors together with a decline in mortality in high-income countries in the past two decades has led to a significant upsurge in the need for secondary prevention of ischaemic heart disease. With this, the role that nonadherence to cardioprotective drugs is having both in terms of clinical outcomes and as a driver of increased healthcare expenditure has become progressively clear.

The CV polypill, which was originally proposed as a strategy to improve accessibility to cardioprotective drugs worldwide, has proven to be a mainstay therapeutic approach to improve medication adherence in CV disease. There is clearly a need for a polypill strategy in the present scenario of CV disease based on improved accessibility, adherence and cost-effectiveness. A great deal of available data support such a strategy, and the various clinical trials that are in progress will help further shape future indications for the CV polypill.

## REFERENCES

- World Health Organization (WHO). *Secondary prevention of noncommunicable diseases in low-and middle-income countries through community-based and health service interventions: World Health Organization-Wellcome Trust meeting report, 1–3 August 2001*. 2002.
- Yusuf S. Two decades of progress in preventing vascular disease. *Lancet* 2002; 360: 2–3.
- Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003; 326: 1419.
- Castellano JM, Sanz G, Ortiz AF et al. A polypill strategy to improve global secondary cardiovascular prevention: From concept to reality. *J Am Coll Cardiol* 2014; 64: 613–621.
- Study TIP. Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): A phase II, double-blind, randomised trial. *Lancet* 2009; 373: 1341–1351.
- Yusuf S, Pais P, Sigamani A et al. Comparison of risk factor reduction and tolerability of a full-dose polypill (with potassium) versus low-dose polypill (polycap) in individuals at high risk of cardiovascular diseases. *Circ Cardiovasc Qual Outcomes* 2012; 5(4): 463–471.
- Webster R, Patel A, Selak V et al. Effectiveness of fixed dose combination medication ('polypills') compared with usual care in patients with cardiovascular disease or at high risk: A prospective, individual patient data meta-analysis of 3140 patients in six countries. *Int J Cardiol* 2016; 205: 147–156.
- Castellano JM, Sanz G, Peñalvo JL et al. A polypill strategy to improve adherence: Results from the FOCUS project. *J Am Coll Cardiol* 2014; 64: 2071–2082.
- Chapman RH, Benner JS, Petrilla AA et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med* 2005; 165: 1147–1152.
- Vrijens B, Vincze G, Kristanto P et al. Adherence to prescribed antihypertensive drug treatments: Longitudinal study of electronically compiled dosing histories. *BMJ* 2008; 336: 1114–1117.
- Corrao G, Zambon A, Parodi A et al. Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: A population-based study in Italy. *J Hypertens* 2008; 26: 819–824.
- Chowdhury R, Khan H, Heydon E et al. Adherence to cardiovascular therapy: A meta-analysis of prevalence and clinical consequences. *Eur Heart J* 2013; 34: 2940–2948.
- Corrao G, Conti V, Merlino L et al. Results of a retrospective database analysis of adherence to statin therapy and risk of nonfatal ischemic heart disease in daily clinical practice in Italy. *Clin Ther* 2010; 32: 300–310.
- Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Rate and determinants of 10-year persistence with antihypertensive drugs. *J Hypertens* 2005; 23: 2101–2107.
- DiMatteo MR. Variations in patients' adherence to medical recommendations: A quantitative review of 50 years of research. *Med Care* 2004; 42: 200–209.
- Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA* 2002; 288: 462–467.
- Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001; 23: 1296–1310.
- Wang T-D, Chen Y-H, Huang C-H et al. Bidirectional adherence changes and associated factors in patients switched from free combinations to equivalent single-pill combinations of antihypertensive drugs. *Hypertension* 2014; 63: 958–967.
- Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: A meta-analysis. *Am J Med* 2007; 120: 713–719.
- Kjellgren KI, Ahlner J, Säljö R. Taking antihypertensive medication—controlling or co-operating with patients? *Int J Cardiol* 1995; 47: 257–268.
- Gerbino PP, Shoheiber O. Adherence patterns among patients treated with fixed-dose combination versus separate antihypertensive agents. *Am J Health Syst Pharm* 2007; 64(12): 1279–1283.
- Banegas JR, López-García E, Dallongeville J et al. Achievement of treatment goals for primary prevention of cardiovascular disease in clinical practice across Europe: The EURIKA Study. *Eur Heart J* 2011; 32: 2143–2152.
- Wood DA. Clinical reality of coronary prevention guidelines: A comparison of EUROASPIRE I and II in nine countries. *Lancet* 2001; 357: 995–1001.
- Beebe TJ, Davern ME, McAlpine DD, Ziegenfuss JK. Comparison of two within-household selection methods in a telephone survey of substance abuse and dependence. *Ann Epidemiol* 2007; 17: 458–463.
- Ford ES, Mokdad AH, Giles WH, Mensah GA. Serum total cholesterol concentrations and awareness, treatment, and control of hypercholesterolemia among US adults. *Circulation* 2003; 107: 2185–2189.
- Brambilla G, Bombelli M, Seravalle G et al. Prevalence and clinical characteristics of patients with true resistant hypertension in central and Eastern Europe: Data from the BP-CARE study. *J Hypertens* 2013; 31: 2018–2024.
- The L. Polypills: An essential medicine for cardiovascular disease. *Lancet (London)* 2017; 389: 984.
- LaFleur J, Oderda GM. Methods to measure patient compliance with medication regimens. *J Pain Palliat Care Pharmacother* 2004; 18: 81–87.
- Sabaté E. *Adherence to Long-Term Therapies: Evidence for Action*. World Health Organization; 2003.
- Castellano JM, Copeland-Halperin R, Fuster V. Aiming at strategies for a complex problem of medical nonadherence. *Global Heart* 2013; 8: 263–271.
- Jackevicius CA, Li P, Tu JV. Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. *Circulation* 2008; 117: 1028–1036.
- Colantonio LD, Huang L, Monda KL et al. Adherence to high-intensity statins following a myocardial infarction hospitalization among Medicare beneficiaries. *JAMA Cardiol* 2017; 2(8): 890–895.
- Bansilal S, Castellano JM, Garrido E et al. Assessing the impact of medication adherence on long-term cardiovascular outcomes. *J Am Coll Cardiol* 2016; 68: 789–801.
- Korhonen MJ, Robinson JG, Annis IE et al. Adherence tradeoff to multiple preventive therapies and all-cause mortality after acute myocardial infarction. *J Am Coll Cardiol* 2017; 70: 1543–1554.
- Sundström J, Hedberg J, Thuresson M et al. Low-dose aspirin discontinuation and risk of cardiovascular events: A Swedish nationwide, population-based cohort study. *Circulation* 2017; 136: 1183–1192.
- Piepoli MF, Hoes AW, Agewall S et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016; 37: 2315–2381.
- Ibanez B, James S, Agewall S et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with



- ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018; 39(2): 119–177.
38. González-Juanatey JR, Mostaza JM, Lobos JM et al. Un paso más allá en la prevención secundaria del riesgo cardiovascular. Documento de consenso del uso clínico del policomprimido. *Rev Española Cardiol* 2016; 69: 547–550.
  39. Vejar M, Abufhele A, Varleta P et al. Adherencia farmacológica y prevención secundaria cardiovascular: una de las principales barreras en el tratamiento de la enfermedad aterosclerótica. Posición del Departamento de Prevención Cardiovascular de SOCHICAR en el uso de la polipíldora en prevención secundaria. *Rev Chilena Cardiol* 2016; 35: 270–282.
  40. Bahiru E, de Cates AN, Farr MR et al. Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases. *Cochrane Database Syst Rev* 2017; 3: CD009868.
  41. Huffman MD, Xavier D, Perel P. Uses of polypills for cardiovascular disease and evidence to date. *Lancet* 2017; 389: 1055–1065.
  42. Yusuf S, Islam S, Chow CK et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): A prospective epidemiological survey. *Lancet* 2011; 378: 1231–1243.
  43. Selak V, Elley CR, Bullen C et al. Effect of fixed dose combination treatment on adherence and risk factor control among patients at high risk of cardiovascular disease: Randomised controlled trial in primary care. *BMJ* 2014; 348: g3318.
  44. Thom S, Poulter N, Field J et al. Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: The UMPIRE randomized clinical trial. *JAMA* 2013; 310: 918–929.
  45. Patel A, Cass A, Peiris D et al. A pragmatic randomized trial of a polypill-based strategy to improve use of indicated preventive treatments in people at high cardiovascular disease risk. *Eur J Prev Cardiol* 2015; 22: 920–930.
  46. Webster R, Castellano JM, Onuma OK. Putting polypills into practice: Challenges and lessons learned. *Lancet* 2017; 389: 1066–1074.
  47. Bitton A, Choudhry NK, Matlin OS et al. The impact of medication adherence on coronary artery disease costs and outcomes: A systematic review. *Am J Med* 2013; 126: 357. e7–357. e27.
  48. Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication adherence leads to lower health care use and costs despite increased drug spending. *Health Affairs* 2011; 30: 91–99.
  49. Becerra V, Gracia A, Desai K et al. Cost-effectiveness and public health benefit of secondary cardiovascular disease prevention from improved adherence using a polypill in the UK. *BMJ Open* 2015; 5: e007111.
  50. Barrios V, Kaskens L, Castellano JM et al. Utilidad de un policomprimido cardiovascular en el tratamiento de pacientes en prevención secundaria en España: Un estudio de coste-efectividad. *Rev Española Cardiol* 2017; 70: 42–49.
  51. Yusuf S, Sleight P, Pogue J et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The heart outcomes prevention evaluation study investigators. *N Engl J Med* 2000; 342: 145–153.
  52. Standards of Medical Care in Diabetes-2017. Summary of revisions. *Diabetes Care*. 2017; 40: S4–S5.
  53. CKD Work Group KDIGO 2012. Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; 3: 1–150.
  54. Marathe PH, Gao HX, Close KL. American Diabetes Association Standards of Medical Care in Diabetes 2017. *J Diabetes* 2017; 1–2.
  55. de Diabetes AL. Guías ALAD sobre el diagnóstico, control y tratamiento de la diabetes mellitus tipo 2 con medicina basada en evidencia. *Revista ALAD* 2013; 52–63.
  56. Volpe M. Should all patients at high cardiovascular risk receive renin-angiotensin system blockers? *QJM* 2012; 105: 11–27.
  57. Lonn EM, Bosch J, López-Jaramillo P et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 2016; 374: 2009–2020.
  58. Yusuf S, Bosch J, Dagenais G et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 2016; 374: 2021–2031.
  59. Yusuf S, Lonn E, Pais P et al. Blood-pressure and cholesterol lowering in persons without cardiovascular disease. *N Engl J Med* 2016; 374: 2032–2043.
  60. Baigent C, Blackwell L, Collins R et al. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: Collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; 373: 1849–1860.
  61. Law MR, Wald NJ, Rudnicka A. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: Systematic review and meta-analysis. *BMJ* 2003; 326: 1423–1424.
  62. Zanchetti A, Thomopoulos C, Parati G. Randomized controlled trials of blood pressure lowering in hypertension. *Circ Res* 2015; 116: 1058–1073.
  63. Elliott WJ. Is fixed combination therapy appropriate for initial hypertension treatment? *Curr Hypertens Rep* 2002; 4: 278–285.
  64. Kotseva K, Wood D, Backer GD et al. EUROASPIRE III: A survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. *Eu J Cardiovasc Prev Rehabil* 2009; 16: 121–137.
  65. Fuster V, Sanz G. A polypill for secondary prevention: Time to move from intellectual debate to action. *Nat Clin Pract Cardiovasc Med* 2007; 4: 173–174.
  66. Sanz G, Fuster V. Fixed-dose combination therapy and secondary cardiovascular prevention: Rationale, selection of drugs and target population. *Nat Clin Pract Cardiovasc Med* 2009; 6: 101–110.
  67. Tamargo J, Castellano JM, Fuster V. The Fuster-CNIC-Ferrer cardiovascular polypill: A polypill for secondary cardiovascular prevention. *Int J Cardiol* 2015; 201: S15–S23.
  68. Coca A, Agabiti-Rosei E, Gifkova R et al. The polypill in cardiovascular prevention: Evidence, limitations and perspective—position paper of the European Society of Hypertension. *J Hypertens* 2017; 35: 1546–1553.
  69. Kolte D, Aronow WS, Banach M. Polypills for the prevention of cardiovascular diseases. *Expert Opin Investig Drugs* 2016; 25: 1255–1264.
  70. Guglietta A, Guerrero M. Issues to consider in the pharmaceutical development of a cardiovascular polypill. *Nat Clin Pract Cardiovasc Med* 2009; 6: 112–119.
  71. Selak V, Bullen C, Stepien S et al. Do polypills lead to neglect of lifestyle risk factors? Findings from an individual participant data meta-analysis among 3140 patients at high risk of cardiovascular disease. *Eur J Prev Cardiol* 2016; 23: 1393–1400.



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# MANAGING ADVERSE EFFECTS AND DRUG INTOLERANCE

# 44

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## INTRODUCTION

Any substance used for medical purposes may lead to adverse effects that can vary from serious life threatening to other minor and quite common complications (1). Given the very high prevalence of arterial hypertension (2–4) and the needed polypharmacy for the treatment of high blood pressure and other concomitant comorbidities, adverse effects are quite often in hypertensive patients (5–7). Most of the time, the management of arterial hypertension is complicated and hampered, not due to the severity of adverse effects, but mainly because they are associated with reduced compliance and adherence to the lifelong drug treatment of blood pressure (8–12). Unfortunately, the more the anti-hypertensive drugs, the less the patient's adherence to the therapy due to increased incidences of adverse events (13). In this respect, wise management of adverse effects and drug intolerance should be integrated in the initial design and individualization of blood pressure treatment strategies in order to increase the efficacy of treatment.

There is wide overlap and difficulty in defining terms such as adverse effect, side effects, adverse events and drug intolerance. For that reason, there is a need to explain, define and simplify the herein applied terminology and approach. Moreover, there are very limited studies and systematic data that focus on the prevalence, and even more, on the management particularly of drug intolerance, as well as of medication's adverse effects in arterial hypertension. In an attempt to provide practical advice, the suggested management strategies are divided into two parts: (i) how to prevent or minimize the expected adverse effects and (ii) how to deal with them upon their presentation.

## ADVERSE EFFECTS: DEFINITION OF COMMONLY USED TERMS AND PREVALENCE IN ARTERIAL HYPERTENSION

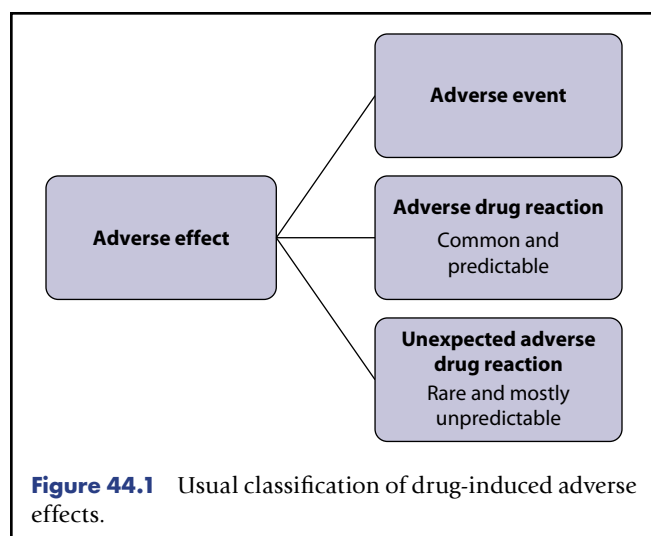
There is substantial overlap and difficulty in defining terms such as adverse effect, side effect and drug intolerance, thus leading to considerable confusion. Moreover, various and different classifications exist, based on different criteria. For reasons of clarity and better clinical

understanding, a brief description of the related terms is needed.

According to the World Health Organization (WHO) (14) and the European Medicines Agency (15,16) adverse effects can be classified (Figure 44.1) as: (i) adverse event, (ii) adverse drug reaction or (iii) unexpected adverse drug reaction. Adverse events are defined as a 'medical occurrence temporally associated with the use of a medicinal product, but not necessarily causally related', like an abnormal laboratory finding, a symptom or a disease (17–19). An adverse drug reaction is a harmful, unintended reaction to medicines which occurs at doses normally used for treatment (14,15,20). The unexpected adverse drug reaction – common or less common – is one which is not consistent, as described in the available summary of product characteristics of the drug (15). Overlapping and fused borders is a quite common case between all the aforementioned terms.

Alternative classification is often used for adverse drug reactions and unexpected drug reactions based on whether they are dose-dependent (also named type A or 'augmented') or non-dose-dependent (also named type B, 'bizarre') reactions. The latter (type B) adverse drug reactions are individual, rare and mostly unpredictable (18,19).

Adverse drug reactions can also be categorized according to their presentation as allergy, drug intolerance or side effect; these terms sometimes overlap. Allergy refers to a systematic response of immunological basis which is understood and studied (17,19,21–24). Side effects are adverse effects of the drug without an immunological background (e.g. cough caused by angiotensin-converting enzyme inhibitors or oedema caused by calcium channel blockers) occurring at normal doses and related to the pharmacological properties of the medication (1,14,15,17). They are quite common and well recognized. Drug intolerance is not so well defined, and its mechanisms of action are not well understood. This type of effect may be due in part to a pharmacological mode of action and in part to the patient's susceptibility, and refers to any subjective or objective adverse reaction not included in the other two categories (25–28). The nocebo effect – that is, the appearance of an adverse effect after exposure to a non-harmful substance – may be a causative factor related to



drug intolerance (29). Special patient characteristics such as anxiety and somatization connected with a nocebo effect can lead to a higher possibility of drug intolerance presentation (27,30). Intolerance to multiple antihypertensive drugs is strongly associated with panic attacks, anxiety and depression, and is also strongly associated with increased psychiatric morbidity (25).

Multiple drug intolerance syndrome refers to the phenomenon of an individual's drug intolerance to more than three drugs with different modes of action (i.e. in hypertensive patients, drug intolerance in more than three classes of antihypertensive drugs) (7,26,28,31–34). In general, multiple drug intolerance syndrome is more likely to be seen in female patients, in patients with documented allergies and diagnosed anxiety disorder, multiple hospital admissions or multiple comorbidities, as well as in the elderly (25,28,35,36). However, no explicit definition of this syndrome has ever been described in any international guidelines regarding the management of arterial hypertension (37–39). This phenomenon seems to be associated with difficult-to-control hypertension, end-organ damage and low quality of life (40).

Data regarding the prevalence of common and less common side effects are extensively provided in the summary of product characteristics of a drug and vary significantly. On the other hand, currently available data on the prevalence (estimated to 2–5% in the general population) (26,28) as well as the clinical significance and implications of drug intolerance and multiple drug intolerance in arterial hypertension (7) is astonishingly limited and quite difficult to obtain.

### MANAGING ADVERSE EFFECTS WHEN TREATING INDIVIDUALS WITH ARTERIAL HYPERTENSION: KEY ISSUES AND OBJECTIVES

The management of adverse effects when treating individuals with elevated blood pressure is particularly important given the fact that arterial hypertension has

certain well-recognized characteristics. First, it is the most common and modifiable cardiovascular risk factor, affecting almost 40% of the general population (2,41,42). Second, it usually requires lifelong drug treatment to optimize cardiovascular risk reduction, and has increased prevalence in the elderly with multiple comorbidities (such as dyslipidemia, diabetes, coronary heart disease and renal impairment) who are in need of multi-drug treatment (6,9,35,36), leading to drug interactions and augmented side effects. And last, it is asymptomatic, thus blood pressure lowering is not accompanied by improved quality of life in most cases, while often the opposite is true due to the emergence of even mild adverse drug effects (40).

As a consequence, the incidence of adverse effects is expected to be closely related to poor adherence to blood pressure-lowering drugs (10–12), as well as to represent an important cause of uncontrolled hypertension (7,26,33) and of increased end-organ damage (32).

Beyond and independently from any difficulties in defining the type of adverse effect in terms of clinical management, adverse effects can be grossly classified in two main groups. The first group includes those adverse effects (common or less common) that are expected to take place; in most of these cases they are related to the mode of action and potentially develop in a dose-dependent manner. Side effects are the most common type of adverse effects belonging to this type of group. The second group includes the unexpected adverse effects which assumingly develop independently from the known mode of drug action (1,20,43).

Given this clinically oriented classification, it is important to note that the management of adverse effects should be integrated in the initial decision-making and design of the individualized blood pressure-lowering treatment strategy in order to meet the following objectives: (i) prevent major and clinically serious adverse effects that can be expected; (ii) prevent minor adverse effects that can be expected, which might however lead to poor compliance and adherence to the drug treatment strategy; (iii) prevent drug treatment discontinuation due to unavoidable expected minor adverse effects; (iv) deal with arisen expected or unexpected adverse effects in the most effective way, preserving, if possible, future use of the responsible class of drug.

### MANAGEMENT OF EXPECTED ADVERSE EFFECTS: PREVENTION OR DRUG CONTINUATION STRATEGIES

While designing an individualized drug treatment strategy, building a balanced and rational approach of expected adverse effects management should include the following steps.

*Step 1: How to prevent major and clinically serious adverse effects that can be expected.*

The most common and less common side effects per class of blood pressure-lowering drugs should be taken into consideration in close accordance with the individual's comorbidities in order to eliminate the incidence of serious (life threatening and/or leading to hospitalization)

**Table 44.1** Common adverse effects of major classes of blood pressure-lowering drugs that should be taken into consideration

| Class of blood pressure-lowering drug    | Commons adverse effects                                                                                                          |
|------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Thiazide-like diuretics                  | Hyponatremia, hypokalaemia, hypercalcaemia, hyperuricemia, decreased insulin sensitivity, photosensitivity, erectile dysfunction |
| $\beta$ -blockers                        | Bronchoconstriction, bradycardia, decreased glucose sensitivity, Raynaud's phenomenon, erectile dysfunction, psoriasis flare     |
| Calcium channel blockers                 | Oedema, bradycardia, flushing, headache, palpitation, constipation                                                               |
| Angiotensin-converting enzyme inhibitors | Angioneurotic oedema, hyperkalaemia, chronic dry cough, decrease in GFR, teratogenesis                                           |
| Angiotensin II receptor blockers         | Hyperkalaemia, decrease in glomerular filtration rate, teratogenesis                                                             |

Source: Modified from Lavan A et al. *Ther Adv Drug Saf* 2018 January; 9(1): 13–23.

adverse effects (5). In a recent meta-analysis of 50 randomized controlled trials, all antihypertensive drug categories had two to three times more adverse events compared to placebo except for the angiotensin receptor blockers, which showed no difference compared to the placebo. In addition, the study shows that they are the only antihypertensive drug class associated with a 29% lower risk of discontinuation due to an adverse event when compared with any of the other classes (13). The major well-known side effects in conjunction with the patient's characteristics are summarized as absolute and relative contradictions (Table 44.1) (37).

Definite and/or potentially harmful combinations of different classes of blood pressure-lowering drugs should also be taken into consideration in order to prevent expected adverse effects (Table 44.2) (37,44).

**Table 44.2** Combinations of classes of blood pressure-lowering drugs that should be taken into consideration upon treatment strategy design in order to prevent the incidence of expected adverse reactions

|                                                              |
|--------------------------------------------------------------|
| Preferred combinations:                                      |
| ■ (ARBs) or (ACEi) or (CCBs) + Diuretics                     |
| ■ (ARBs) or (ACEi) + CCBs                                    |
| Possible combinations:                                       |
| ■ (ARBs) or (ACEi) or (CCBs) or (Diuretics) + BBs            |
| ■ (ARBs) or (ACEi) or (CCBs) or (Diuretics) or (BBs) + other |
| Not recommended combinations:                                |
| ■ ARBs + ACEi                                                |

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARBs, type 1 angiotensin-receptor blockers; BBs, beta-blockers; CCBs, calcium channel blockers; other, other antihypertensives.

*Step 2: How to prevent minor adverse effects that can be expected, which might however lead to poor compliance and adherence to the drug treatment strategy.*

Minor adverse effects are a cause of poor compliance and low adherence to the predefined treatment strategy. They can be minimized on the basis of the following treatment rules that should be taken into consideration from the beginning of the treatment design.

1. Use of usual-dose combination of two different classes of blood pressure-lowering drugs, instead of a single drug at maximal dose. Efficient data suggest that this strategy provides greater effective blood pressure-lowering effect with fewer side effects (44,45) due to (i) the fewer dose-dependent adverse effects (33,46), and (ii) the complementary actions of the different classes of drugs, which might counterbalance and eliminate the side effects of the other drug class (46).
2. Use of low (or very low) dose combination of two different classes of blood pressure-lowering drugs at usual doses each, instead of a single drug at a usual dose. Although this novel strategy lacks sufficient data, it is supported by some studies (33,44,47–50), showing that it provides at least the same blood pressure-lowering effect with fewer side effects due to (i) minimal or milder dose-dependent adverse effects, and (ii) complementary actions of the drug that eliminate the side effect of the other class of drug. The use of more than two (i.e. three or four) in ultra-low doses is also under investigation as an alternative that might lead to fewer dose-dependent side effects (51,52); however, the possibility that this strategy might be related to increased type B unexpected drug reactions or drug intolerance should be also taken into consideration and further investigated.
3. Optimization of chronotherapy to minimize side effects, such as orthostatic or postprandial hypotension, can be considered. Although as a general therapeutic rule, blood pressure-lowering drugs with 24-hour action are recommended to be used together (at least up to three) once daily – usually in the morning – it is reasonable to consider in selected cases: (i) the use of drugs with shorter half-life, (ii) in two or three doses/day in order to achieve the optimal chronotherapy (53,54).
4. Consider and discuss the effect of seasonal changes and changes in environmental temperature on the blood pressure level and drug side effects; schedule predefined seasonal consultations in order to minimize related side effects by modifying accordingly – if needed – drug doses, especially of diuretics and calcium channel blockers (55,56).
5. Discuss in detail the role of diet and of particular nutrients (sodium, potassium, calcium) in relation to drug treatment, and modify accordingly in order to avoid potential side effects (57).

*Step 3: How to prevent drug treatment discontinuation due to unavoidable minor adverse effects that can be expected.*

Provided that steps 1 and 2 have been taken into consideration, each individual should be explicitly informed upon drug treatment initiation regarding the most



common and expected side effects, which are associated with very mild and potentially temporary symptoms related to the initiation of the drugs. Patient awareness regarding their non-harmful nature, the reassurance on their reversibility upon drug discontinuation, as well as clear guidance about when further contact with the treating physician is needed, are reasonable actions in daily clinical practice in order to minimize drug treatment discontinuation, patient's low adherence to optimal drug use (daily uptake in the proposed dose) and patient lost to the upcoming follow-up. Particularly, in difficult to treat or resistance hypertension – in need of four or five different classes of blood pressure-lowering drugs in order to achieve blood pressure treatment goals – the cost of any expected unavoidable minor side effect (e.g. mild – or even substantial – ankle oedema due to calcium channel blocker use) versus the benefit of effective blood pressure control and cardiovascular risk reduction should be clearly addressed. We should bear in mind, though, that for any single drug addition to the therapy, 4% more patients discontinue their medication in 5 years (13).

In adherence with good clinical practice, in any case physicians should inform all patients regarding the likelihood of an adverse effect while on blood pressure-lowering medication. Interacting with hypertensive individuals and educating them on: (i) the need for and importance of antihypertensive treatment; (ii) the mode of drug administration and actions; (iii) the possible adverse effects in order to recognize in an early stage any drug-related adverse effect; and (iv) the pitfalls of dosage or medication altering without expert consultation, are factors associated with better patient compliance (12).

*Step 4: How to deal with a developed expected adverse effect.*

When dealing with an expected adverse event that has already occurred, the physician should take into consideration the following. It is highly reasonable to consider that an expected adverse event is directly and causally related to specific type of drug. It is reasonable that in the case of a minor adverse effect that is dose dependent and/or can be prevented with the precautions discussed above in steps 1–3, the drug might be reintroduced (after temporary discontinuation) in the treatment strategy, potentially at a lower dose, if considered to be indispensable. This option should be discussed in detail with the hypertensive individual.

In cases of adverse effects efficiently classified as severe allergic reaction of immunological basis, a class contradiction should be labelled (22,23).

### MANAGEMENT OF DEVELOPED UNEXPECTED ADVERSE EFFECTS: TREATMENT STRATEGIES

The management of unexpected adverse effects can be dealt with only upon patient complaint, since they are not anticipated. Given the fact that they cannot be easily documented, have undetermined low prevalence (7,58) and unknown mechanism of action, a treatment algorithm cannot be easily introduced. Drug intolerance, if not recognized in an early stage, will lead to patient nonadherence to treatment, resulting in uncontrolled hypertension with end-organ damage. Most drug intolerance reactions are mild, and the physician should discuss

with the individual the possibility of drug re-challenge, as well as the possibility to try the use of other drugs of the same class before permanently omitting this specific class of medication.

Multiple drug intolerance in blood pressure-lowering drugs is a rare but difficult to handle condition. There is only one available study regarding the management of unpredictable responses of antihypertensive drugs, based on a retrospective analysis (33) in a small population with multiple drug intolerance in blood pressure-lowering drugs. We propose a modified treatment algorithm for multiple drug intolerance, based on a five-step approach focusing on alternative blood pressure-lowering methods and/or alternative route of drug administration until the patient is relieved from the symptoms:

*Step 1: Introduction of alternative blood pressure-lowering methods (beyond drugs, diet and exercise) such as device-guided breathing and transcendental meditation. (Step 1 can be used in combination with all the following steps.)*

*Step 2: Use of fractional doses of conventional medications by halving or quartering tablets; use of combinations (double, triple etc.).*

*Step 3: Use of liquid drug formulations.*

*Step 4: Use of transdermal antihypertensive medication.*

*Step 5: Consider use of alternative blood pressure-lowering regimens.*

Individuals with intolerance to multiple antihypertensive drugs may have panic attacks, anxiety and depression disorders (25) and might benefit from psychiatric evaluation.

## CONCLUSIONS AND PERSPECTIVES

Adverse effects caused by blood pressure-lowering drugs are not uncommon but are usually mild. They are important because they are associated with treatment discontinuation or low adherence. Preventive management of side effects should be integrated in the initial design of treatment strategies. Future studies focusing on the potential superiority of ultra-low doses of multidrug combinations to minimize side effects should be carried out. A five-step algorithm for the management of multiple drug intolerance in arterial hypertension is proposed; however very limited data on this issue are available and future studies should shed more light on this phenomenon.

## REFERENCES

1. Smith W. Adverse drug reactions – allergy? side-effect? intolerance? *Aust Fam Physician* 2013; 42(1–2): 12–16.
2. Kearney PM, Whelton M, Reynolds K, Whelton PK, He J. Worldwide prevalence of hypertension: A systematic review. *J Hypertens* 2004; 22(1): 11–19.
3. Costanzo S, Di Castelnuovo A, Zito F et al. Prevalence, awareness, treatment and control of hypertension in healthy unrelated male-female pairs of European regions: The dietary habit profile in European communities with different risk of myocardial infarction – the impact of migration as a model of gene-environment interaction project. *J Hypertens* 2008; 26(12): 2303–2311.
4. Pereira M, Lunet N, Azevedo A, Barros H. Differences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. *J Hypertens* 2009; 27(5): 963–975.
5. Rende P, Paletta L, Gallelli G et al. Retrospective evaluation of adverse drug reactions induced by antihypertensive treatment. *J Pharmacol Pharmacother* 2013; 4(1): S47–S50.

6. Sato I, Akazawa M. Polypharmacy and adverse drug reactions in Japanese elderly taking antihypertensives: A retrospective database study. *Drug Healthc Patient Saf* 2013; 5: 143–150.
7. Neculau AE, Rogozea LM, Andreescu O, Jinga L, Dinu EA, Tint D. Multiple drug-intolerant hypertension. *Am J Ther* 2017; 24(5): e588–e591.
8. Ross SD, Akhras KS, Zhang S, Rozinsky M, Nalysnyk L. Discontinuation of antihypertensive drugs due to adverse events: A systematic review and meta-analysis. *Pharmacotherapy* 2001; 21(8): 940–953.
9. Butt TF, Branch RL, Beesley L, Martin U. Managing hypertension in the very elderly: Effect of adverse drug reactions (ADRs) on achieving targets. *J Hum Hypertens* 2010; 24(8): 514–518.
10. Marshall IJ, Wolfe CD, McKevitt C. Lay perspectives on hypertension and drug adherence: Systematic review of qualitative research. *BMJ* 2012; 345: e3953.
11. Hyman DJ. Hypertension: Does polypharmacy lead to nonadherence or nonadherence to polypharmacy? *Hypertension* 2017; 69(6): 1017–e1018.
12. Gupta P, Patel P, Strauch B et al. Risk factors for nonadherence to antihypertensive treatment. *Hypertension* 2017; 69(6): 1113–1120.
13. Thomopoulos C. et al. Effects of blood-pressure-lowering treatment in hypertension: 9. Discontinuations for adverse events attributed to different classes of antihypertensive drugs: Meta-analyses of randomized trials. *J Hypertens* 2016; 34: 1921–1932.
14. International drug monitoring. The role of national centres. Report of a WHO meeting *World Health Organ Tech Rep Ser* 1972; 498: 1–25.
15. European Medicines Agency. Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95). TGA Publications Office. 2000.
16. Dal Pan GJ, Arlett PR. The US Food and Drug Administration-European Medicines Agency collaboration in pharmacovigilance: Common objectives and common challenges. *Drug Saf* 2015; 38(1): 13–15.
17. Aronson JK, Ferner RE. Clarification of terminology in drug safety. *Drug Saf* 2005; 28(10): 851–870.
18. Brockow K, Przybilla B, Aberer W et al. Guideline for the diagnosis of drug hypersensitivity reactions: S2K-Guideline of the German Society for Allergy and Clinical Immunology (DGAKI) and the German Dermatological Society (DDG) in collaboration with the Association of German Allergologists (AeDA), the German Society for Pediatric Allergy and Environmental Medicine (GPA), the German Contact Dermatitis Research Group (DKG), the Swiss Society for Allergy and Immunology (SGAI), the Austrian Society for Allergy and Immunology (OGAI), the German Academy of Allergy and Environmental Medicine (DAAU), the German Center for Documentation of Severe Skin Reactions and the German Federal Institute for Drugs and Medical Products (BfArM). *Allergo J Int* 2015; 24(3): 94–105.
19. Sadreddini HA, Starkey ES. Drug allergy: Diagnosis and management of drug allergy in adults, children and young people; a look at NICE guidance. *Arch Dis Child Educ Pract Ed* 2016; 101(5): 239–242.
20. Edwards IR, Aronson JK. Adverse drug reactions: Definitions, diagnosis, and management. *Lancet* 2000; 356(9237): 1255–1259.
21. Solensky R, Khan DA et al. Drug allergy: An updated practice parameter. *Ann Allergy Asthma Immunol* 2010; 105(4): 259–273.
22. Demoly P, Adkinson NF, Brockow K et al. International Consensus on drug allergy. *Allergy* 2014; 69(4): 420–437.
23. Dworzynski K, Arden-Jones M, Nasser S. Diagnosis and management of drug allergy in adults, children and young people: Summary of NICE guidance. *BMJ* 2014; 349: g4852.
24. Wheatley LM, Plaut M, Schwaninger JM et al. Report from the National Institute of Allergy and Infectious Diseases workshop on drug allergy. *J Allergy Clin Immunol* 2015; 136(2): 262–g4271 e2.
25. Davies SJ, Jackson PR, Ramsay LE, Ghahramani P. Drug intolerance due to nonspecific adverse effects related to psychiatric morbidity in hypertensive patients. *Arch Intern Med* 2003; 163(5): 592–600.
26. Schiavino D, Nucera E, Roncallo C et al. Multiple-drug intolerance syndrome: Clinical findings and usefulness of challenge tests. *Ann Allergy Asthma Immunol* 2007; 99(2): 136–142.
27. Hassel JC, Danner D, Hassel AJ. Psychosomatic or allergic symptoms? High levels for somatization in patients with drug intolerance. *J Dermatol* 2011; 38(10): 959–965.
28. Omer HM, Hodson J, Thomas SK, Coleman JJ. Multiple drug intolerance syndrome: A large-scale retrospective study. *Drug Saf* 2014; 37(12): 1037–1045.
29. Hauser W, Hansen E, Enck P. Nocebo phenomena in medicine: Their relevance in everyday clinical practice. *Dtsch Arztebl Int* 2012; 109(26): 459–465.
30. De Pasquale T, Nucera E, Boccascino R et al. Allergy and psychologic evaluations of patients with multiple drug intolerance syndrome. *Intern Emerg Med* 2012; 7(1): 41–47.
31. Macy E, Ho NJ. Multiple drug intolerance syndrome: Prevalence, clinical characteristics, and management. *Ann Allergy Asthma Immunol* 2012; 108(2): 88–93.
32. Saxena M, Antoniou S, Hamed N et al. Multiple drug-intolerant hypertension: A case series utilising a novel-treatment algorithm. *Br J Gen Pract* 2016; 66(645): e285–e287.
33. Antoniou S, Saxena M, Hamed N et al. Management of hypertensive patients with multiple drug intolerances: A single-center experience of a novel treatment algorithm. *J Clin Hypertens (Greenwich)* 2016; 18(2): 129–138.
34. Pichler WJ, Srinoulprasert Y, Yun J, Hausmann O. Multiple drug hypersensitivity. *Int Arch Allergy Immunol* 2017; 172(3): 129–138.
35. Petrovic M, van der Cammen T, Onder G. Adverse drug reactions in older people: Detection and prevention. *Drugs Aging* 2012; 29(6): 453–462.
36. Lavan A, Eustace J, Dahly D et al. Incident adverse drug reactions in geriatric inpatients: A multicentred observational study. *Ther Adv Drug Saf* 2018; 9(1): 13–23.
37. Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; 34(28): 2159–2219.
38. James PA, Oparil S, Carter BL et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311(5): 507–520.
39. Whelton PK, Carey RM, Aronow WS et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018; 71(19): e127–e248.
40. Dahlof C. Well-being (quality of life) in connection with hypertensive treatment. *Clin Cardiol* 1991; 14(2): 97–103.
41. Wolf-Maier K, Cooper RS, Banegas JR et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA* 2003; 289(18): 2363–2369.
42. Cruickshank JK. Worldwide prevalence, awareness, treatment and control of hypertension. *J Hypertens* 2004; 22(1): 21–24.
43. Patton K, Borshoff DC. Adverse drug reactions. *Anaesthesia* 2018; 73(Suppl 1): 76–84.
44. Mark H et al. Low-dose combination blood pressure pharmacotherapy to improve treatment effectiveness, safety, and efficiency. *JAMA* 2018; 320(6): 1–2.
45. Rochlani Y, Khan MH, Banach M, Aronow WS. Are two drugs better than one? A review of combination therapies for hypertension. *Expert Opin Pharmacother* 2017; 18(4): 377–386.
46. de la Sierra A. Mitigation of calcium channel blocker-related oedema in hypertension by antagonists of the renin-angiotensin system. *J Hum Hypertens* 2009; 23(8): 503–511.
47. Laurent S. Clinical benefit of very-low-dose perindopril-indapamide combination in hypertension. *J Hypertens* 2001; 19(4): S9–S14.
48. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low-dose combination treatment with blood pressure lowering drugs: Analysis of 354 randomised trials. *BMJ* 2003; 326(7404): 1427–1428.
49. Sung SH, Wu TC, Lin SJ, Chen JW. Efficacy of a very-low-dose combination of perindopril and indapamide–preterax compared with cilazapril monotherapy in patients with inadequate blood pressure control—a randomized, double-blind, add-on study. *J Chin Med Assoc* 2008; 71(5): 247–253.
50. Laurent S, Parati G, Chazova I et al. Randomized evaluation of a novel, fixed-dose combination of perindopril 3.5 mg/amlodipine 2.5 mg as a first-step treatment in hypertension. *J Hypertens* 2015; 33(3): 653–661; discussion 62.
51. Chow CK, Thakkar J, Bennett A et al. Quarter-dose quadruple combination therapy for initial treatment of hypertension: Placebo-controlled, crossover, randomised trial and systematic review. *Lancet* 2017; 389(10073): 1035–1042.
52. Bennett A, Chow CK, Chou M et al. Efficacy and safety of quarter-dose blood pressure-lowering agents: A systematic review and meta-analysis of randomized controlled trials. *Hypertension* 2017; 70(1): 85–93.
53. Schillaci G, Battista F, Settimi L, Schillaci L, Pucci G. Antihypertensive drug treatment and circadian blood pressure rhythm: A review of the role of chronotherapy in hypertension. *Curr Pharm Des* 2015; 21(6): 756–772.

54. Hermida RC, Ayala DE, Smolensky MH, Fernandez JR, Mojon A, Portaluppi F. Chronotherapy with conventional blood pressure medications improves management of hypertension and reduces cardiovascular and stroke risks. *Hypertens Res* 2016; 39(5): 277–292.
55. Modesti PA, Morabito M, Massetti L et al. Seasonal blood pressure changes: An independent relationship with temperature and daylight hours. *Hypertension* 2013; 61(4): 908–914.
56. Sato N, Saijo Y, Sasagawa Y et al. Visit-to-visit variability and seasonal variation in blood pressure: Combination of Antihypertensive Therapy in the Elderly, Multicenter Investigation (CAMUI) Trial subanalysis. *Clin Exp Hypertens* 2015; 37(5): 411–419.
57. Appel LJ, Moore TJ, Obarzanek E et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* 1997; 336(16): 1117–1124.
58. McDowell SE, Thomas SK, Coleman JJ, Aronson JK, Ferner RE. A practical guide to monitoring for adverse drug reactions during antihypertensive drug therapy. *J R Soc Med* 2013; 106(3): 87–95.

# ADHERENCE TO TREATMENT IN HYPERTENSION

# 45

Michel Burnier

## INTRODUCTION

In developed countries, only half of patients with hypertension are treated, and less than half of those who are treated reach the recommended blood pressure (BP) targets (1). After decades of efforts to improve the detection and the management of hypertensive patients in the population, and despite the accumulation of evidence from clinical trials demonstrating the clinical benefits of lowering BP in hypertension, unfortunately we remain confronted with the same figures. This suggests that the important gap between the rate of BP control obtained in clinical trials and the rate reported in national surveys reflecting real life remains unchanged over the years (2). Many factors can explain this gap, among which therapeutic inertia and drug adherence are probably the most important. Today, a number of drugs are available to lower BP in hypertension. The numerous compounds belonging to the four major antihypertensive drug classes (diuretics, calcium antagonists, blockers of the renin-angiotensin system and beta-blockers) effectively reduce BP. However, it is obvious that if drugs are not prescribed adequately by physicians and not taken correctly by patients, they cannot be effective. In addition, they will certainly not provide the expected benefits in terms of cardiovascular protection. Clinical inertia is a form of medical nonadherence. Results of surveys have suggested that medical inertia may occur because physicians do not adhere strictly to the official recommendations and set the targets too high, or because they have a wrong perception of the BP control of their patients, overestimating the quality of the control (3). Of note, medical inertia and poor adherence to therapy are not issues specific of the management of hypertension (4,5). In an analysis of drug adherence in a large group of patients treated for the primary and secondary prevention of cardiovascular diseases, a low adherence to therapy was found with antihypertensive agents as well as with lipid-lowering treatments and aspirin, suggesting that poor adherence is common to most if not all chronic diseases (4) (Figure 45.1).

## DEFINITIONS AND TAXONOMY OF ADHERENCE TO TREATMENT

Several terms can be found in the literature which describe different aspects of drug adherence, such as *adherence*, *compliance*, *concordance* or *persistence*. These terms are sometimes used as synonyms, and what they actually represent is not always well understood. According to the World Health Organization, adherence is the extent to which a person's behaviour – taking medication, following a diet and/or executing lifestyle changes – corresponds with agreed recommendations from a healthcare provider. A particular effort has been done in the field of adherence to clarify the terms and their definitions. To this purpose, a consensus paper has been written which presents a taxonomy in which adherence to medications is conceptualized, based on behavioural and pharmacological science and support quantifiable parameters (6). Thus, *adherence to medication* is the process by which patients take their medications as prescribed. Adherence has three components: *initiation*, *implementation* and *discontinuation*. *Initiation* is the time from when the prescription is given until first dose of the medication is taken. The implementation of the dosing regimen is defined as the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken. *Discontinuation* marks the end of therapy, when the next dose to be taken is omitted and no more doses are taken thereafter. *Persistence* is the length of time between initiation and the last dose that immediately precedes discontinuation. Practically, three types of deviation from prescribed dosing instructions are particularly frequent – that, is non-initiation, short persistence and poor execution of the dosing regimen. In clinical practice, about 24% of patients, including those with hypertension, never start their treatment, illustrating the importance of the non-initiation process (7,8). Short persistence, which consists of all patients ceasing their engagement with the dosing regimen on their own initiative, is definitively the most common problem of adherence to treatment, with 50% of

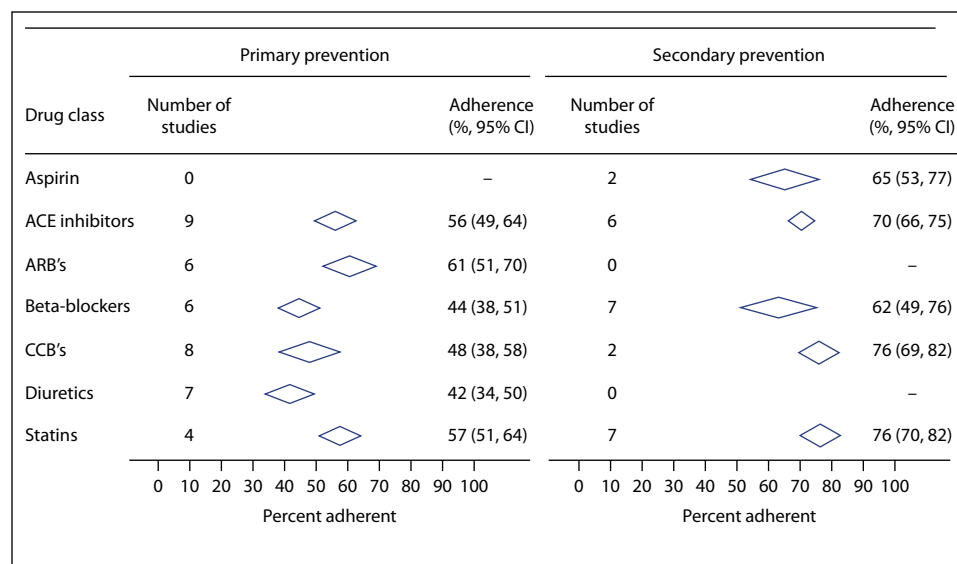


**Figure 45.1** Persistence to therapy in primary and secondary cardiovascular prevention. (From Naderi SH et al. *Am J Med* 2012; 125(9): 88–7e1.)

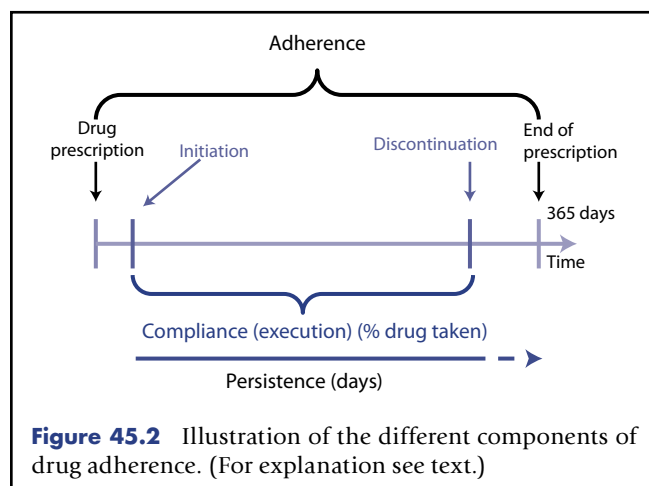


**Figure 45.2** Illustration of the different components of drug adherence. (For explanation see text.)

patients being non-persistent at 1 year in clinical studies (9) as well as in clinical practice (10). In the Swedish survey, the worst persistence occurred among patients aged 30–49 years and in those older than 80 years (10). Finally, *poor execution* is illustrated by lapses in implementation (or execution), which are the typical consequence of forgetfulness or negligence resulting in more or less prolonged periods of treatment interruptions. Each of these aspects of adherence to medication has a direct impact on the quality of BP control in hypertension, the most critical ones being non-initiation and lack of persistence. The different processes are illustrated in Figure 45.2.

## METHODS OF MEASURING DRUG ADHERENCE

Many methods to assess whether an individual has taken the prescribed pills, thereby enabling estimation of drug

adherence, exist. As shown in Table 45.1, all have advantages and limitations. The simplest one is undoubtedly a careful interview of the patient, leading to the physician's impression of what the patient is actually doing with his/her medications. This method is imprecise, and recent studies have suggested that it is no better than tossing a coin (11). The only exceptions are patients who did not initiate their treatment and admit that they did not accept the treatment for whatever reason. Thus, the physician's impression is a very weak indicator of a patient's level of adherence.

Currently, more than 50 questionnaires have been created to assess adherence to therapy in various clinical situations (12). However, no single method performs well on all criteria. These questionnaires are used prominently in clinical studies, and their results tend to overestimate adherence, as patients tend to forget the episodes when no medication was taken. A popular questionnaire is the Morisky questionnaire, which is easy and rapid to use in practice in its simplified version (13). However, when compared to electronic measurements of adherence, the Morisky questionnaire has been found to overestimate drug adherence as well. This questionnaire is also not adequate for repeated measurements.

The most common method of assessing drug adherence in clinical trials is the pill count. This method provides a relatively good overview of what has been taken by the patient during a time period, but again the general trend of this method is an overestimation. This is due to the tendency of patients to return empty boxes. Indeed, patients receiving more pills than needed often return an empty box. In large epidemiological studies, careful monitoring of prescription refills is sometimes used. This approach enables calculation of the percentage of days covered by the prescriptions, thus providing a rough estimate of drug adherence over a long time period (14). This may be useful when electronic monitoring of drug prescriptions is available in pharmacies. Such continuous registries may be helpful to evaluate drug persistence and the risk factors



**Table 45.1** Advantages and limits of methods used to assess adherence to therapy

|            |                   | Clinical<br>assessment | Questionnaire | Pill<br>count | Prescription<br>refills | DOT | Electronic<br>monitoring | Drugs<br>assays | Telemonitoring |
|------------|-------------------|------------------------|---------------|---------------|-------------------------|-----|--------------------------|-----------------|----------------|
| Advantages | Accuracy          | ↓↓↓                    | ↓↓↓           | ↓↓            | ↓↓                      | ↑↑↑ | ↑↑                       | ↑↑              | ↑              |
|            | Objectivity       | ↓↓↓                    | ↓↓↓           | ↓↓            | ↓↓                      | ↑↑↑ | ↑↑                       | ↑↑              | ↑↑             |
|            | Feasibility       | ↑↑↑                    | ↑↑↑           | ↑↑            | ↓                       | ↓↓↓ | ↑                        | ↓               | ↓↓             |
|            | Educational value | ↓↓↓                    | ↑             | ↑             | —                       | ↑   | ↑↑↑                      | ↑↑              | ↑↑             |
| Limits     | Workload          | ↓↓↓                    | ↑             | ↑             | ↑↑                      | ↑↑  | ↑↑                       | ↑↑              | ↑↑             |
|            | White-coat effect | —                      | —             | ↑↑↑           | —                       | —   | ↑                        | ↑↑↑             | ↑↑             |
|            | Manipulability    | ↓↓↓                    | ↑↑            | ↑↑↑           | ↑↑                      | ↓↓↓ | ↑↑↑                      | ↓↓              | ↓↓             |
|            | Cost              | ↓↓↓                    | ↓             | ↓             | ↑                       | ↑↑  | ↑↑                       | ↑↑↑             | ↑↑↑            |

Abbreviation: DOT, direct observed treatment.

associated with a poor adherence (10,15). However, this approach assumes that patients take their drugs adequately every day, which is not always the case. Moreover, patients may use different pharmacies to obtain their medications. Thus, the monitoring system should cover all sources of medication delivery.

Two methods actually provide very interesting and reliable information on drug adherence: electronic monitoring, and direct measurements of plasma or urinary drug levels. The former gives very interesting dynamic information on adherence and is based essentially on the fact that if the pillbox is not open, the drug is not taken. However, it does not prove ingestion when the box was opened (16). In contrast, direct measurements of drugs ascertain drug intake, but the information obtained with drug levels is only punctual (17). The fact that electronic monitoring systems do not prove the medication was taken is often seen as a major limitation of these devices. Yet in our experience, one has to admit that it is rare that a patient opens the pillbox every day and throws the medication away over several months. Thus, information gathered with the electronic monitoring is quite reliable provided the monitoring is performed long enough (at least several months). As far as drug measurements are concerned, positive results confirm that some drug has been taken, but physicians obtain no information on when the drug was taken and how often doses were missed between consultations, and this may limit the interpretation of the results. In fact, although measurements of drug levels tend to become popular, for example in patients with resistant hypertension (17–23), this approach may be affected by the *white-coat adherence* bias, according to which patients tend to improve their adherence a few days before and after a consultation (24). Thus if patients are informed that blood or urine will be taken to measure drug levels, which should be done ethically, the method may be of limited interest. Moreover, chemical methods are costly and labour intensive. Nonetheless, recent studies using this methodological approach without informing patients have clearly demonstrated that drug adherence is particularly low among patients with resistant hypertension. Interestingly, measuring drug levels appears to improve adherence to therapy, as shown in Figure 45.3 (25,26). These results come from a retrospective analysis of about 300 urine samples

from nonadherent hypertensive patients from the United Kingdom and the Czech Republic (26).

As noted in a recent review, the ideal method to assess drug adherence in clinical practice should ‘provide a reliable capture, storage, analysis, and communication of dosing history data in ways that make it difficult or impossible for patients or trial staff to censor or otherwise manipulate the data’ (16). Nowadays, three methods are close to fulfilling these criteria: the retrospective analysis of prescription refill records, analysis of chemical markers of drug exposure, and automatic electronic monitoring of adherence.

## RISK FACTORS OF POOR ADHERENCE IN HYPERTENSION

Hypertension is a disease than can be treated but rarely cured. Thus patients must be informed that therapy will be maintained for the rest of their life. The long-term management of hypertension generates many obstacles that may affect the capacity of patients to stay on therapy. As illustrated in Table 45.2, these obstacles can find their origin in the treatment itself, in the patient’s beliefs, in the attitude of the physician and in the quality of the healthcare system. The first obstacle is acceptance of the diagnosis and the difficulty for some patients to initiate a lifelong treatment program for a silent disease. Depending on the quality of the information they receive, patients may not be motivated. This is the reason persistence to antihypertensive therapy is low in newly treated patients and declines further in following years. One study, in which persistence with antihypertensive therapy fell to 75% in the first 6 months after treatment and continued to decline over the next 3 years to 55%, illustrated this observation perfectly (27). Later, patients are confronted with the first side effects of prescribed drugs. In the absence of symptoms before treatment, side effects may not be accepted and tolerated. With time, the treatment scheme may become more complex. Indeed, it is well recognized that 70% of patients will need more than one drug to reach the target BP recommended by guidelines. However, the more drugs patients receive, the lower the persistence (28,29). Eventually, patients may be exposed to delayed side effects such as sexual dysfunction. These factors will further decrease the motivation

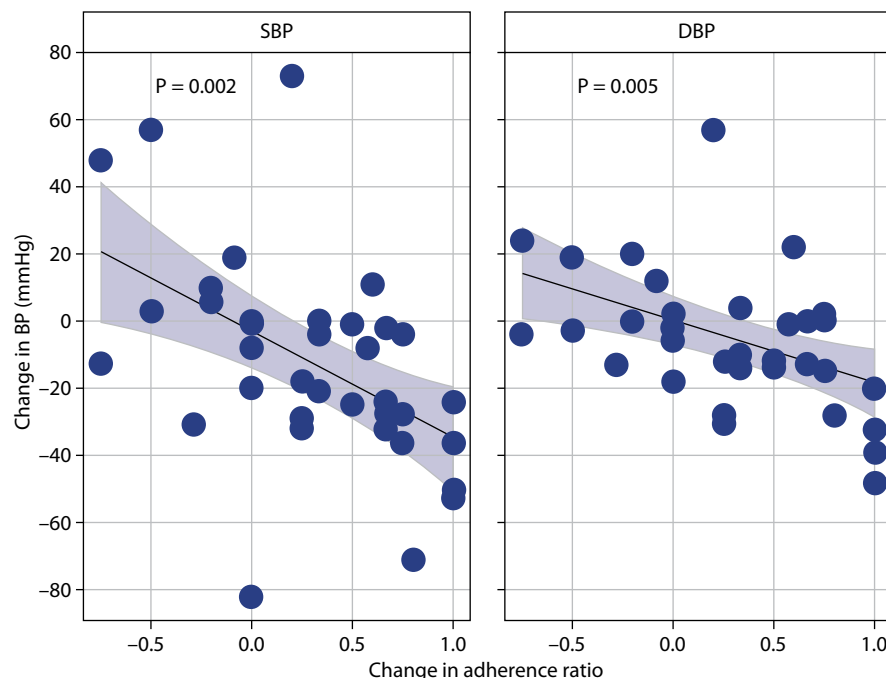


**Figure 45.3** Changes in blood pressure in relation to changes in urinary adherence ratio based on urinary drug levels (ratio of detected to prescribed antihypertensive medications). (From Gupta P et al. *Hypertension* 2017; 70(5): 104–1048.)

to remain under treatment, and for many patients the necessity of pursuing the treatment will be questioned, leading in most cases to a discontinuation of therapy.

Interestingly, a recent meta-analysis by Simpson et al. has shown that patients with excellent adherence to therapy have a globally positive attitude towards all preventive recommendations for a better health (30). Thus, these patients with healthy behaviours have a better survival even if they receive a placebo, as demonstrated recently in the post hoc analysis of a heart failure trial (31). However, it is also important to note that in some cases, good adherence may have also damaging effects if the drug has serious adverse effects and the patient continues to take them. Two examples are the use of nonsteroidal anti-inflammatory drugs and antiarrhythmic agents (30).

**Table 45.2** Factors associated with an increased risk of poor adherence

- Age and sex (young men at higher risk)
- Elderly patients with cognitive impairment
- Personal and family beliefs
- Asymptomatic nature of hypertension
- Understanding of the benefits of treatment
- Lower socioeconomic status
- Cost of treatments and copayments
- Severity of disease
- Number of drugs and complexity of treatment
- Drug tolerability (acute and long-term side effects)
- Efficacy on blood pressure control
- Family support
- Physician-patient relationship
- Depression and comorbidities

Besides these therapy-related factors, several other barriers and risk factors for interrupting treatment have been identified (Table 45.2). These barriers come from the patient him/herself but also from the family, the physician, the nature of the treatment and the healthcare system. The main factors affecting long-term adherence are depression, other comorbidities, personal as well as family beliefs on hypertension and on the necessity of treatment, lack of knowledge about hypertension, cost of medications, use of alternative medicines, memory problems in elderly patients and poor quality of life.

Several studies have clearly identified the characteristics of patients at high risk of nonadherence to treatment. These are essentially young, active men, hypertensive patients of African American origin, elderly patients with cognitive dysfunction and a low income (32,33). Gender does not seem to be a major determinant in all circumstances, even though studies have suggested that adherence to therapy is better in females than males. Differences in comorbidities, types of treatment and severity of hypertension may account for some of the gender differences reported in many surveys (34). The same is true for educational level. The healthcare system per se, and particularly the copayment, also has a major impact on the long-term persistence of patients treated for hypertension. Thus it is very important for physicians to identify these high-risk factors, as strategies can be developed to prevent any interruption of therapy, as will be discussed later in this review.

## ADHERENCE IN HYPERTENSION

It is well recognized that adherence to medication is an important determinant of the BP response to treatment and

hence of the clinical benefits of antihypertensive therapies. In the last two decades, many clinical studies and meta-analyses have assessed drug adherence in patients with essential hypertension and also in patients with uncontrolled hypertension or apparent resistant hypertension (17,23,33,35). In all conditions, adherence to therapy was highly variable but particularly low among patients with uncontrolled hypertension, with almost 80% nonadherence in this subgroup (33). In many early studies, the assessment was done using the Medication Event Monitoring System (MEMS) which enables one to follow adherence on a day-to-day basis for a long time period (35,36). These studies were aimed at not only defining adherence in hypertension but also at investigating the ability of the monitoring system to support drug adherence. Interestingly, the same observations were made more recently with measurement of drugs in the urine (20,23). The finding of a high adherence in many studies may be due to the measurement bias, as adherence tends to increase as soon as it is measured. With the use of the MEMS system, which provides a dosing history, many interesting aspects of the adherence process can be seen. The first and probably the most important one is that drug adherence is a very *dynamic process*, which cannot be summarized with a single number. Indeed, patients are adherent for some periods and less adherent at other times, for example during weekends and holidays. Second, it is very difficult to define a cutoff point above which drug adherence is sufficient and acceptable. Indeed, in the literature, the arbitrary cutoff of 80% is often used to define good adherence, but it is obvious that 80% can be obtained in several ways with different clinical impacts – for example, missing 1 day every 5 days or 1 week every 5 weeks. Moreover, the impact of missed doses on BP control and risk reduction depends largely on the pharmacological profile of the prescribed drug, and particularly on the duration of action (37). This is why prescribing long-acting medications in patients at risk of poor adherence is generally recommended. Thirdly, many investigators have tried to demonstrate a correlation between the level of BP achieved under treatment and the percentage of doses taken. Associations between adherence to antihypertensive drug therapy and BP control have been obtained but they have generally been very weak (38–40). In fact, there are many good reasons why this type of correlation should not be very high. Indeed, high BP values are frequent in nonadherent hypertensive patients, but also in adherent patients insufficiently or inadequately treated.

Despite many of these limitations, evidence gathered from large databases usually confirms that patients with good adherence have better BP control (33,39). Moreover, highly persistent hypertensive patients have a greater reduction of their cardiovascular risk than those interrupting their treatment (41,42). Finally, good adherence to antihypertensive medications has been associated with a significant reduction of the risk of cardiovascular events such as coronary heart disease, congestive heart failure and cerebral diseases (29,43–45).

## ADHERENCE IN RESISTANT HYPERTENSION

Apparent resistance to therapy is one clinical situation in which the question of drug adherence becomes particularly important. When the prescribed antihypertensive drugs do

not lower BP as expected, physicians have only two choices: either the patient is a true nonresponder to therapy or the patient is not taking his/her drug as recommended thus being a non-adherer. In the former situation, the patient has a true resistance to treatment, whereas in the latter, it is only apparent or pseudo-resistance. In the absence of adequate tools to measure adherence, physicians have only one option, and that is to consider the patient as a nonresponder. Therefore, they will probably increase the drug doses or add another drug in order to achieve the therapeutic targets. However, if adherence is the real problem, adding new drugs will only aggravate the situation. One study actually confirmed that nonadherent hypertensive patients have not only a higher BP but also a greater number of prescribed drugs (22).

With the recent development of new interventional approaches for the management of patients with resistant hypertension, a renewed interest for resistant hypertension and its causes has emerged, including adherence to therapy (46,47). Several analyses have investigated the potential causes of apparent resistance to drug therapy in hypertension. Not surprisingly, poor drug adherence emerged as one important factor of pseudo-resistance (17). Yet, as of today, the true incidence of poor adherence remains largely unknown in this patient population because adherence is not measured adequately. Thus, published figures range between 10–50% (17,18,20,23,38). In our experience, using electronic monitoring of drug adherence, about one-third of patients with resistant hypertension had adherence problems leading to uncontrolled hypertension (38,48). More recently, several studies have been conducted among hypertensive patients with uncontrolled BP or candidates to renal denervation to assess drug adherence using measurements of either urinary or blood concentrations of drugs (18,20,21,23). They confirmed high percentages of partial or total nonadherence (sometimes greater than 50%). These figures are important and may well be underestimations, as they do not take into account the white-coat adherence phenomenon discussed earlier in this review (24). In hypertensive patients with coronary heart disease, resistant hypertension also appears to be common (38%) and to be associated with a worst cardiovascular prognosis (49).

In any case, poor adherence is a real concern in resistant hypertension. Unfortunately, adherence to therapy remains largely underdiagnosed in clinical studies despite the availability of adequate noninvasive methods. In recent studies, some investigators have used the directly observed treatment (DOT) or 'tablet feed', which is commonly used in the management of tuberculosis, to evaluate the role of poor adherence in mediating uncontrolled BP (50). Although a small number of patients participated in some of these studies, the studies clearly showed that many patients normalize their BP when the treatment is given under control. In a larger group of 102 patients, 65% of patients achieved a systolic BP <140 mmHg at any point immediately prior to or after drug ingestion (51). In the United Kingdom, clinics dedicated to the DOT system have been installed with some success (52). Thus, taken together, these new data confirm that adherence to the drug regimen is a critical issue in resistant hypertension. We believe that a good assessment of adherence in patients not responding to drug therapy is essential in order to make rational therapeutic decisions. To this purpose, methodologies to monitor adherence should be implemented in hypertension reference centres as suggested recently (17). Yet as of today, the main limitation is the lack of cheap and easy-to-use methods of monitoring

adherence in clinical practice. Measurements of urinary or plasma drug levels and electronic monitoring are the most adequate methods that can be recommended today.

## STRATEGIES TO IMPROVE DRUG ADHERENCE IN HYPERTENSION

A critical meta-analysis of the multiple strategies to improve drug adherence in hypertension and chronic diseases has been published recently (53). In this analysis, the standardized mean difference effect size is only 0.290 comparing treatment and control groups. Larger effect sizes are found for habit-based and behavioural-targeted (vs. cognitive-focused) interventions. The most effective interventions appear to be those delivered face to face by physicians or by pharmacists and administered directly to patients. Effect sizes are smaller in studies with older participants. Interestingly, the authors recommend focusing interventions on behavioural strategies, especially habit-based interventions, rather than on cognitive strategies designed to change knowledge and beliefs. As illustrated in Table 45.3,

**Table 45.3** Approaches and methods available to support the adherence to therapy

| <i>Treatment</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>■ Simplifying treatment schedules (e.g. twice to once daily dosing)</li> <li>■ Reduce number of drugs using single-pill combinations</li> <li>■ Prefer long-acting agents and drugs with the least side effects</li> <li>■ Use drugs in favourable packages with calendar (blister vs. bottle)</li> <li>■ Use of reminders (medication dispenser, organizers, telemonitoring ...)</li> <li>■ Stop any unnecessary treatment</li> </ul>                                                                                                                                                                                                                                            |
| <i>Healthcare providers</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <ul style="list-style-type: none"> <li>■ Regular discussions on adherence and its barriers</li> <li>■ Provide clear instructions to patients</li> <li>■ Collaborate with other providers (pharmacists, nurses, ...)</li> <li>■ Healthcare provider education on adherence (medical students, physicians, nurses, pharmacists...)</li> <li>■ Improve communication skills of healthcare partners</li> <li>■ Good interpersonal relationship between provider and patient</li> <li>■ Increase the frequency of appointments in case of low adherence</li> <li>■ Regular monitoring of adherence during treatment (electronic monitoring, urinary drug levels...)</li> <li>■ Give positive feedbacks to patients</li> </ul> |
| <i>Patient empowerment</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <ul style="list-style-type: none"> <li>■ Educate patient to self-management</li> <li>■ Discuss the patient's beliefs and barriers to adherence</li> <li>■ Use of home BP monitoring</li> <li>■ Use of tele-monitoring systems</li> <li>■ Propose tips for maintaining adherence (at work, during holidays...)</li> <li>■ Increase the family involvement and education</li> </ul>                                                                                                                                                                                                                                                                                                                                        |
| <i>Other approaches</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <ul style="list-style-type: none"> <li>■ Improve the access to care</li> <li>■ Reduce or suppress co-payments</li> <li>■ Increase the social support</li> <li>■ Counselling</li> <li>■ Home visits</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

the approaches may include the patient, the therapeutic regimen, physicians and the healthcare system.

The first and certainly the most important step to support long-term adherence is to carefully inform the patient on the goals of therapy and on the means to achieve the therapeutic objectives. In order to be motivated and stay on therapy, patients need to know the risks linked to their disease, and to consider them as serious. This has been well illustrated in patients with chronic kidney diseases who may need to take up to 15 pills a day (54). In this study, the patient's perception of the burden of the disease was a major determinant of persistence. Patients have to know the BP goals and the effects expected from therapy. They also have to be informed on the means to achieve these goals, to acquire specific competences and to develop a set of personal strategies to reach the targets, to cope with the disease and to autoregulate their actions. Finally, they have to believe in their personal efficacy. Thus, among all strategies to improve adherence, empowerment of the patient is critical (55). In this respect, a recent study has shown that self-monitoring and even self-titration of drugs by patients results in a significantly lower BP control at 1 year even in high cardiovascular risk patients (56). Home BP monitoring (HBPM) is also a good recommendation in patients who have difficulties with their treatment and are at high risk of not staying on therapy. A systematic review of the published literature on the effects of HBPM on medication adherence has confirmed the benefits of this approach on adherence to therapy (57). Today, the use of home BP monitoring is increasing, and this strategy is strongly endorsed by the European Society of Hypertension (58). On their side, physicians also need to be motivated and should avoid medical inertia and show patients that they are eager to achieve the BP goals in order to preserve their patients' health (59).

One can also act on the prescribed regimen to support drug adherence over time. Both the number of drugs patients receive and the dosing frequency have a major impact on persistence (60–62). Several studies have demonstrated that simplifying the drug regimen with the use of fixed-dose combinations has a positive impact on adherence and persistence (63–67). A recent meta-analysis confirmed that simplification of therapy is an effective therapeutic approach in hypertension that improves adherence, though the impact on BP control is relatively modest (66). This finding was confirmed in a Cochrane analysis of different strategies to improve adherence in hypertension (68). However, a recent survey among Swedish hypertensive patients has shown that in patients started on a combination therapy, drug persistence at 2 years was not superior, and surprisingly, perhaps even inferior (32). Regarding the adaptation of drug therapy, the prescription of combinations of long-acting drugs, which blunt the effect of isolated missed doses, is preferable. Studies have shown that BP is more likely to remain adequately controlled despite the omission of one or two doses if the antihypertensive drug has a long half-life (37).

Several other tools can support drug adherence in hypertensive patients (69). These include the use of organizers, recalls using telephones or emails, rewards, special packages and behavioural interventions. All of these tools have been shown to have some positive effect on drug adherence, but the effect size is rather small, in the order of 4–11%. The most effective way to support drug



adherence and improve persistence during a long period is probably to monitor drug adherence continuously, for example with an electronic monitoring system such as the MEMS, or with the use of repeated drug measurements. The use of such devices enables one to obtain real data on patient adherence and allows a discussion between the physician and patient on adherence data. Unfortunately, the MEMS device is used essentially in clinical trials and very few hospitals or reference centres are using them as a clinical tool. However, the MEMS device can be used in clinical centres for a relatively modest cost (16). In recent years, much experience has been gained with the use of urinary or blood drug monitoring. Data have now revealed that these drug measurements are not only useful to detect nonadherence but they have a major impact on adherence, increasing the persistence and hence the quality of the BP control, as discussed previously and illustrated in Figure 45.3 (25,26).

The development of communication technologies may also help to support the adherence to therapy by improving the link between patients and their physicians (70). Thus, telemonitoring of BP measured at home by the patient with the possibility of an interaction between the caregiver and the patient in case of a problem seems to be a cost-effective way to support drug adherence and lower BP (71). Large trials using this approach are ongoing.

In some countries, a multidisciplinary approach which includes pharmacists and/or nurses is favoured to increase adherence and hence to ameliorate clinical parameters (72–74). The multidisciplinary approach is very interesting and effective, but it often faces major problems, such as the collaboration between physicians and pharmacists in some countries, and more importantly, the reimbursement of pharmacists' activities by the healthcare system. Moreover, the cost-effectiveness of this approach is regularly questioned, as well as that of sustained nursing support (75,76).

Finally, the health system and its ability to reimburse activities linked to the management of drug adherence and to limit the copayment of drugs in patients with financial difficulties is an important issue (77). In a recent review of the literature, reduced medication copayments were associated with improved hypertension control and treatment adherence. This was evaluated mainly in North American settings (78).

## CONCLUSIONS

Although cardiovascular mortality tends to decline in developed countries, hypertension remains a major risk factor for the development of cardiovascular events. Today, there is no new antihypertensive drug to be launched that will improve our ability to treat and control BP in the population. New invasive techniques, such as renal denervation and carotid baroreflex stimulation, have not yet found their place in the long-term management of hypertension. In any case, they will be limited to the treatment of patients with resistant hypertension and whether they will affect drug adherence is not known. Therefore, physicians have no other choice but to use available drugs, including fixed-dose combinations. In this context, one must address the issue of drug adherence and persistence. BP control in the population will

be improved only by recruiting more untreated hypertensive patients and supporting drug adherence. To this purpose, there is an urgent need to develop new methodologies or devices enabling detection and monitoring of drug adherence in order to provide physicians with reliable information on which they can build their therapy and support their patients in their efforts to achieve their therapeutic goals, and hence reduce the risk of cardiovascular complications.

## REFERENCES

1. Rahimi K, Emdin CA, MacMahon S. The epidemiology of blood pressure and its worldwide management. *Circ Res* 2015; 116(6): 925–936.
2. Burnier M. Blood pressure control and the implementation of guidelines in clinical practice: Can we fill the gap? *J Hypertens* 2002; 20(7): 1251–1253.
3. Hyman DJ, Pavlik VN. Self-reported hypertension treatment practices among primary care physicians: Blood pressure thresholds, drug choices, and the role of guidelines and evidence-based medicine. *Arch Intern Med* 2000; 160(15): 228–236.
4. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: Meta-analysis on 376,162 patients. *Am J Med* 2012; 125(9): 882–887.e1.
5. Aujoulat I, Jacquemin P, Rietzschel E et al. Factors associated with clinical inertia: An integrative review. *Adv Med Educ Pract* 2014; 5: 119–125.
6. Vrijens B, De Geest S, Hughes DA et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol* 2012; 73(5): 691–705.
7. Fischer MA, Choudhry NK, Brill G et al. Trouble getting started: Predictors of primary medication nonadherence. *Am J Med* 2011; 124(11): 1081.e9–22.
8. Fischer MA, Stedman MR, Lii J et al. Primary medication non-adherence: Analysis of 195,930 electronic prescriptions. *J Gen Intern Med* 2010; 25(4): 284–290.
9. Vrijens B, Vincze G, Kristanto P et al. Adherence to prescribed antihypertensive drug treatments: Longitudinal study of electronically compiled dosing histories. *BMJ* 2008; 336(7653): 111–117.
10. Qvarnstrom M, Kahan T, Kieler H et al. Persistence to antihypertensive drug treatment in Swedish primary healthcare. *Eur J Clin Pharmacol* 2013; 69(11): 1955–1964.
11. Meddings J, Kerr EA, Heisler M et al. Physician assessments of medication adherence and decisions to intensify medications for patients with uncontrolled blood pressure: Still no better than a coin toss. *BMC Health Serv Res* 2012; 12: 270.
12. Nguyen TM, La Caze A, Cottrell N. What are validated self-report adherence scales really measuring?: A systematic review. *Br J Clin Pharmacol* 2014; 77(3): 427–445.
13. Morisky DE, Ang A, Krousel-Wood M et al. Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens (Greenwich)* 2008; 10(5): 348–354.
14. Halpern MT, Khan ZM, Schmier JK et al. Recommendations for evaluating compliance and persistence with hypertension therapy using retrospective data. *Hypertension* 2006; 47(6): 1039–1048.
15. Hasselstrom J, Zarrinkoub R, Holmquist C et al. The Swedish Primary Care Cardiovascular Database (SPCCD): 74 751 hypertensive primary care patients. *Blood Press* 2014; 23(2): 116–125.
16. Burnier M, Wuerzner G, Struijker-Boudier H et al. Measuring, analyzing, and managing drug adherence in resistant hypertension. *Hypertension* 2013; 62(2): 218–225.
17. Berra E, Azizi M, Capron A et al. Evaluation of adherence should become an integral part of assessment of patients with apparently treatment-resistant hypertension. *Hypertension* 2016; 68(2): 297–306.
18. Jung O, Gechter JL, Wunder C et al. Resistant hypertension? Assessment of adherence by toxicological urine analysis. *J Hypertens* 2013; 31(4): 766–774.
19. Schmieder RE, Ott C, Schmid A et al. Adherence to antihypertensive medication in treatment-resistant hypertension undergoing renal denervation. *J Am Heart Assoc* 2016; 5(2): pii: e002343.
20. Tomaszewski M, White C, Patel P et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. *Heart* 2014; 100(11): 855–861.



21. Strauch B, Petr  k O, Zelinka T et al. Precise assessment of noncompliance with the antihypertensive therapy in patients with resistant hypertension using toxicological serum analysis. *J Hypertens* 2013; 31(12): 2455–2461.
22. Hamdidouche I, Jullien V, Boutouyrie P et al. Routine urinary detection of antihypertensive drugs for systematic evaluation of adherence to treatment in hypertensive patients. *J Hypertens* 2017; 35(9): 1891–1898.
23. Hamdidouche I, Jullien V, Boutouyrie P et al. Drug adherence in hypertension: From methodological issues to cardiovascular outcomes. *J Hypertens* 2017; 35(6): 1133–1144.
24. Cramer JA, Scheyer RD, Mattson RH. Compliance declines between clinic visits. *Arch Intern Med* 1990; 150(7): 1509–1510.
25. Brinker S, Pandey A, Ayers C et al. Therapeutic drug monitoring facilitates blood pressure control in resistant hypertension. *J Am Coll Cardiol* 2014; 63(8): 834–835.
26. Gupta P, Patel P, Strauch B et al. Biochemical screening for nonadherence is associated with blood pressure reduction and improvement in adherence. *Hypertension* 2017; 70(5): 1042–1048.
27. Perreault S, Lamarre D, Blais L et al. Persistence with treatment in newly treated middle-aged patients with essential hypertension. *Ann Pharmacother* 2005; 39(9): 1401–1408.
28. Xie L, Frech-Tamas F, Marrett E et al. A medication adherence and persistence comparison of hypertensive patients treated with single-, double- and triple-pill combination therapy. *Curr Med Res Opin* 2014; 30(12): 2415–2422.
29. Mazzaglia G, Ambrosioni E, Alacqua M et al. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. *Circulation* 2009; 120(16): 159–605.
30. Simpson SH, Eurich DT, Majumdar SR et al. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ* 2006; 333(7557): 1598–1605.
31. Granger BB, Swedberg K, Ekman I et al. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: Double-blind, randomised, controlled clinical trial. *Lancet* 2005; 366(9502): 2005–2011.
32. Qvarnstrom M, Kahan T, Kieler H et al. Persistence to antihypertensive drug classes: A cohort study using the Swedish Primary Care Cardiovascular Database (SPCCD). *Medicine (Baltimore)* 2016; 95(40): e4908.
33. Abegaz TM, Shehab A, Gebreyohannes EA et al. Nonadherence to antihypertensive drugs: A systematic review and meta-analysis. *Medicine (Baltimore)* 2017; 96(4): e5641.
34. Ljungman C, Kahan T, Sch  ler L et al. Gender differences in antihypertensive drug treatment: Results from the Swedish Primary Care Cardiovascular Database (SPCCD). *J Am Soc Hypertens* 2014; 8(12): 882–890.
35. Christensen A, Osterberg LG, Hansen EH. Electronic monitoring of patient adherence to oral antihypertensive medical treatment: A systematic review. *J Hypertens* 2009; 27(8): 1540–1551.
36. Wetzels GE, Nelemans P, Schouten J et al. Electronic monitoring of adherence as a tool to improve blood pressure control. A randomized controlled trial. *Am J Hypertens* 2007; 20(2): 119–125.
37. Lowy A, Munk VC, Ong SH et al. Effects on blood pressure and cardiovascular risk of variations in patients' adherence to prescribed antihypertensive drugs: Role of duration of drug action. *Int J Clin Pract* 2011; 65(1): 41–53.
38. Bertholet N, Favrat B, Fallab-Stubi CL et al. Why objective monitoring of compliance is important in the management of hypertension. *J Clin Hypertens (Greenwich)* 2000; 2(4): 258–262.
39. Bramley TJ, Gerbino PP, Nightengale BS et al. Relationship of blood pressure control to adherence with antihypertensive monotherapy in 13 managed care organizations. *J Manag Care Pharm* 2006; 12(3): 239–245.
40. Mallion JM, Dutrey-Dupagne C, Vaur L et al. Benefits of electronic pillboxes in evaluating treatment compliance of patients with mild to moderate hypertension. *J Hypertens* 1996; 14(1): 137–144.
41. Corrao G, Parodi A, Nicotra F et al. Better compliance to antihypertensive medications reduces cardiovascular risk. *J Hypertens* 2011; 29(3): 610–618.
42. Burnier M, Brede Y, Lowy A. Impact of prolonged antihypertensive duration of action on predicted clinical outcomes in imperfectly adherent patients: Comparison of aliskiren, irbesartan and ramipril. *Int J Clin Pract* 2011; 65(2): 127–133.
43. Perreault S, Dragomir A, Roy L et al. Adherence level of antihypertensive agents in coronary artery disease. *Br J Clin Pharmacol* 2010; 69(1): 74–84.
44. Perreault S, Dragomir A, White M et al. Better adherence to antihypertensive agents and risk reduction of chronic heart failure. *J Intern Med* 2009; 266(2): 207–218.
45. Perreault S, Yu AXX, Cote R et al. Adherence to antihypertensive agents after ischemic stroke and risk of cardiovascular outcomes. *Neurology* 2012; 79(20): 2037–2043.
46. Mahfoud F, Schmieder RE, Azizi M et al. Proceedings from the 2nd European Clinical Consensus Conference for device-based therapies for hypertension: State of the art and considerations for the future. *Eur Heart J* 2017; 38(44): 3272–3281.
47. Lobo MD, Sobotka PA, Pathak A. Interventional procedures and future drug therapy for hypertension. *Eur Heart J* 2017; 38(15): 1101–1111.
48. Burnier M, Schneider MP, Chiol  ro A et al. Electronic compliance monitoring in resistant hypertension: The basis for rational therapeutic decisions. *J Hypertens* 2001; 19(2): 335–341.
49. Smith SM, Gong Y, Handberg E et al. Predictors and outcomes of resistant hypertension among patients with coronary artery disease and hypertension. *J Hypertens* 2014; 32(3): 635–643.
50. Fadl Elmula FE, Hoffmann P, Larstorp AC et al. Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension. *Hypertension* 2014; 63(5): 991–999.
51. Bunker J, Chang C-L, Chapman N et al. True resistant hypertension following observed drug ingestion: A systematic evaluation. *J Clin Hypertens (Greenwich)* 2017; 19(3): 250–255.
52. Hameed MA, Tebbit L, Jacques N et al. Non-adherence to antihypertensive medication is very common among resistant hypertensives: Results of a directly observed therapy clinic. *J Hum Hypertens* 2016; 30(2): 83–89.
53. Conn VS, Ruppert TM. Medication adherence outcomes of 771 intervention trials: Systematic review and meta-analysis. *Prev Med* 2017; 99: 269–276.
54. Neri L, Martini A, Andreucci VE et al. Regimen complexity and prescription adherence in dialysis patients. *Am J Nephrol* 2011; 34(1): 71–76.
55. Gwady-Sridhar FH, Manias E, Lal L et al. Impact of interventions on medication adherence and blood pressure control in patients with essential hypertension: A systematic review by the ISPOR medication adherence and persistence special interest group. *Value Health* 2013; 16(5): 863–871.
56. McManus RJ, Mant J, Haque MS et al. Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: The TASMEN-SR randomized clinical trial. *JAMA* 2014; 312(8): 799–808.
57. Ogedegbe G, Schoenthaler A. A systematic review of the effects of home blood pressure monitoring on medication adherence. *J Clin Hypertens (Greenwich)* 2006; 8(3): 174–180.
58. Parati G, Stergiou GS, Asmar R et al. European Society of Hypertension practice guidelines for home blood pressure monitoring. *J Hum Hypertens* 2010; 24(12): 779–785.
59. Marquez-Contreras E, Gil-Guill  n VF, De La Figueroa-Von Wichmann M et al. Non-compliance and inertia in hypertensive Spaniards at high cardiovascular risk: CUMPLE study. *Curr Med Res Opin* 2014; 30(1): 11–17.
60. Coleman CI, Limone B, Sobieraj DM et al. Dosing frequency and medication adherence in chronic disease. *J Manag Care Pharm* 2012; 18(7): 527–539.
61. Isk  djian M, Einarson TR, MacKeigan LD et al. Relationship between daily dose frequency and adherence to antihypertensive pharmacotherapy: Evidence from a meta-analysis. *Clin Ther* 2002; 24(2): 302–316.
62. Burnier M, Brown RE, Ong SH et al. Issues in blood pressure control and the potential role of single-pill combination therapies. *Int J Clin Pract* 2009; 63(5): 790–798.
63. Burnier M. Medication adherence and persistence as the cornerstone of effective antihypertensive therapy. *Am J Hypertens* 2006; 19(11): 1190–1196.
64. Castellano JM, Sanz G, Pe  lva JL et al. A polypill strategy to improve adherence: Results from FOCUS (Fixed-dose Combination Drug for Secondary Cardiovascular Prevention) Project. *J Am Coll Cardiol* 2014 Nov 18–25; 64(20): 2071–2082.
65. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: A meta-analysis. *Hypertension* 2010; 55(2): 399–407.
66. Selak V, Elley CR, Bullen C et al. Effect of fixed dose combination treatment on adherence and risk factor control among patients at high risk of cardiovascular disease: Randomised controlled trial in primary care. *BMJ* 2014; 348: g3318.

67. Simons LA, Chung E, Ortiz M. Long-term persistence with single-pill, fixed-dose combination therapy versus two pills of amlodipine and perindopril for hypertension: Australian experience. *Curr Med Res Opin* 2017; 33(10): 1783–1787.
68. Schroeder K, Fahey T, Ebrahim S. Interventions for improving adherence to treatment in patients with high blood pressure in ambulatory settings. *Cochrane Database Syst Rev* 2004; (2): CD004804.
69. Peterson AM, Takiya L, Finley R. Meta-analysis of trials of interventions to improve medication adherence. *Am J Health Syst Pharm* 2003; 60(7): 657–665.
70. Omboni S, Gazzola T, Carabelli G et al. Clinical usefulness and cost effectiveness of home blood pressure telemonitoring: Meta-analysis of randomized controlled studies. *J Hypertens* 2013; 31(3): 455–467; discussion 466–468.
71. Albini F, Xiaoqiu L, Torlasco C et al. An ICT and mobile health integrated approach to optimize patients' education on hypertension and its management by physicians: The Patients Optimal Strategy of Treatment (POST) pilot study. *Conf Proc IEEE Eng Med Biol Soc* 2016; 2016: 517–520.
72. Santschi V, Rodondi N, Bugnon O et al. Impact of electronic monitoring of drug adherence on blood pressure control in primary care: A cluster 1-month randomised controlled study. *Eur J Intern Med* 2008; 19(6): 427–434.
73. Santschi V, Chiolerio A, Burnand B et al. Impact of pharmacist care in the management of cardiovascular disease risk factors: A systematic review and meta-analysis of randomized trials. *Arch Intern Med* 2011; 171(16): 1441–1453.
74. Santschi V, Chiolerio A, Colosimo AL et al. Improving blood pressure control through pharmacist interventions: A meta-analysis of randomized controlled trials. *J Am Heart Assoc* 2014; 3(2): e000718.
75. Van Zuilen AD, Wetzels JF, Bots ML et al. MASTERPLAN: Study of the role of nurse practitioners in a multifactorial intervention to reduce cardiovascular risk in chronic kidney disease patients. *J Nephrol* 2008; 21(3): 261–267.
76. Chapman RH, Ferrufino CP, Kowal SL et al. The cost and effectiveness of adherence-improving interventions for antihypertensive and lipid-lowering drugs\*. *Int J Clin Pract* 2010; 64(2): 169–181.
77. Despres F, Forget A, Kettani FZ et al. Impact of patient reimbursement timing and patient out-of-pocket expenses on medication adherence in patients covered by private drug insurance plans. *J Manag Care Spec Pharm* 2016; 22(5): 539–547.
78. Maimaris W, Paty J, Perel P et al. The influence of health systems on hypertension awareness, treatment, and control: A systematic literature review. *PLOS MED* 2013; 10(7): e1001490.



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*Giuseppe Mancia*

## INTRODUCTION

Several studies have shown that, although antihypertensive treatment reduces the incidence of cardiovascular (CV) events in almost any demographic and clinical condition in which blood pressure (BP) is elevated, the CV risk of treated hypertensive patients is never fully normalized; that is, the risk of fatal and nonfatal CV events remains higher, sometimes markedly so, than in the control normotensive population (1–3) even if BP is reduced to or almost to the recommended BP target (4), as shown by the long-term cumulative incidence of mortality and coronary outcomes in normotensives and treated hypertensive patients of Figure 46.1.

The incomplete CV protection of apparently well treated hypertensive patients, and thus their abnormally high 'residual' risk, may have a genetic component, namely an association of a high BP with a genetic profile that makes a CV risk portion unmodifiable with BP manipulations. There are, however, other possible factors which can be potentially addressed by suitable intervention strategies (Table 46.1). These factors are discussed in this chapter for their rationale and evidence.

## POOR CONTROL OF ASSOCIATED CV RISK FACTORS

It is a longstanding notion that hypertension is frequently accompanied by other CV risk factors, which makes the overall risk of this condition most often of a multifactorial nature. This was documented decades ago by the Framingham Study, which showed that in hypertensive men and women, obesity, insulin-resistant diabetes and dyslipidaemias were present in more than 80% of the cases, the majority of which exhibited two or more additional risk factors (5). It has since been confirmed by many other studies which have also reported that, regardless of the age, gender and ethnicity of the patients, a BP elevation is frequently accompanied by a high prevalence of glucose-related, lipid-related and body weight-related CV risk factors (6–8), often leading to an overall high CV risk (9). Indeed, evidence has been extended to show that the association

between high BP and metabolic risk factors cannot be simply explained by the high prevalence of these conditions in most populations because (i) in normotensive type 2 diabetic patients, new-onset hypertension is more frequent than in normotensive nondiabetic patients (10), (ii) dyslipidemic individuals may have a greater incidence of new-onset hypertension than normolipidemic ones (11) and (iii) the relationship between hypertension and alterations in glucose and lipid metabolism has a quantitative value. This was shown years ago in the PAMELA population in which alterations of body mass index, prevalence of type 2 diabetes and blood glucose values or prevalence of dyslipidaemias and serum cholesterol values all increased progressively as office BP, home BP or 24-h BP mean increased from the lowest to the highest quintile (12).

An abundant body of evidence also exists that in the hypertensive population, therapeutic control of additional risk factors is limited (6,13) and that a multifactorial risk profile makes control of the individual risk components worse than that achieved when only one risk factor is present (14,15). It is also clear that lipid- and glucose-lowering treatments exert their protective effect regardless of the BP of the patients; that is, that both therapeutic interventions exert a similar protective effect in both normotensive and hypertensive individuals (10,16), including hypertensive patients in whom antihypertensive treatment has achieved BP control. For lipid-lowering treatment this has been clearly documented by the ASCOT trial, in which hypertensive patients in whom treatment had reduced systolic BP to <140 mmHg (138 mmHg), statin administration led to a significant reduction of CV events (stroke – 27%; coronary heart disease – 29%; CV disease – 21%), compared to placebo (17). There seems therefore to be no question that better control of associated risk factors can further reduce the risk of hypertensive patients below the value achieved by BP control, with a favourable effect on residual risk.

## INAPPROPRIATE TARGET BP VALUES

The 2013 European guidelines on hypertension recommended antihypertensive treatment to lower BP to <140/90 mmHg in the general hypertensive population,

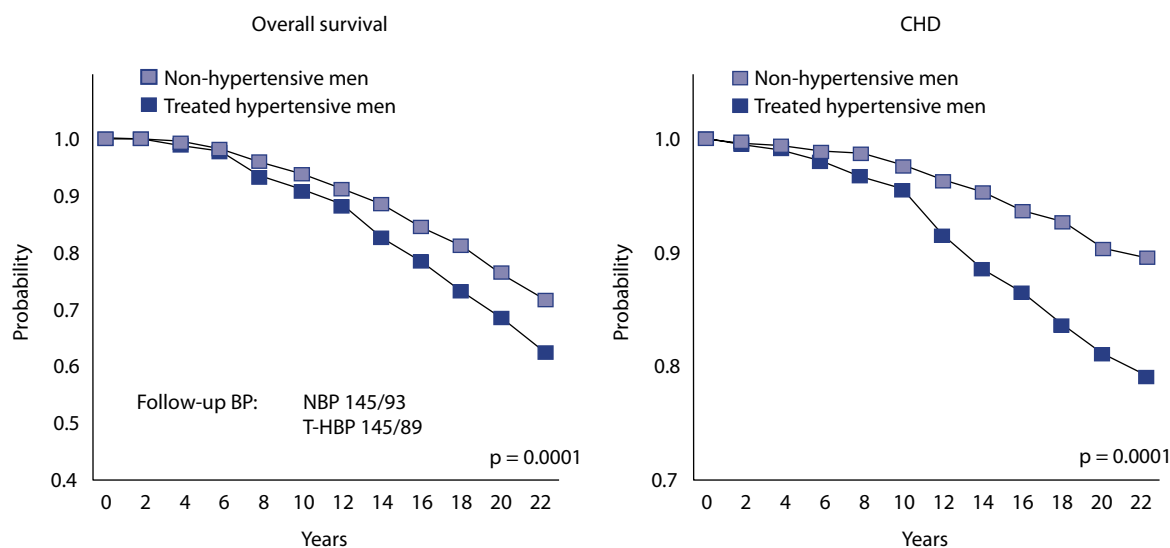


**Figure 46.1** Long-term (>20 years) cumulative probability of overall survival and survival free from coronary events (CHD) in 686 men treated for hypertension and almost at BP target compared to 8100 men taken from the General Prevention Study in Sweden. Abbreviations: T-HBP, treatment-high blood pressure; NBP, normal blood pressure. (From Andersson OK et al. *BMJ* 1998 July 18; 317(7152): 167–171, by permission.)

with a more conservative attitude in the elderly in which the recommended systolic target is between 140 and 150 mmHg (4). More recent trials, as well as recent large meta-analyses, suggest that lowering BP to values just above or below 130/80 mmHg may incrementally protect most patients with high BP (18,19), and that this may be the case also if in the older patient strata (>65 years of age) systolic BP is reduced to the 130–139 rather than to the 140–149 mmHg range (20). More rigorous BP targets may thus represent another means to reduce the residual risk of treated hypertensive individuals, although with the caveat that in real life an indiscriminate adoption of lower BP targets may generate inconveniences that can potentially reduce their benefits. First, in patient subgroups, for example, those with coronary heart disease, systolic BP reductions to <130 mmHg have been reported to be accompanied by a J-curve-like increase in the incidence of most CV events (21), a phenomenon that seems to be common to most hypertensives if BP is reduced to <120/70 mmHg (22). Second, BP reductions and lower BP targets are accompanied by a marked increase in the incidence of serious side effects (20,22,23), with adverse consequences for patients' health. One example is the increased incidence of renal ischemia associated with lower BP targets, which leads to the development of chronic kidney disease (20), ultimately increasing CV risk as well (24). Another is the

increased incidence of orthostatic hypotension, which may increase the risk of injurious falls and bone fractures, particularly in the elderly (25). Third, serious side effects are also the most important reason for treatment discontinuation (26), which is also more frequent at lower BP targets (27) and is known to be accompanied by a marked increase of disease and mortality (28). Ideally, the optimal BP target should be established on an individual basis, a goal which is unfortunately beyond what cardiovascular medicine can presently do. The position of the new European guidelines on optimal target BP values for treatment is presented in a separate chapter.

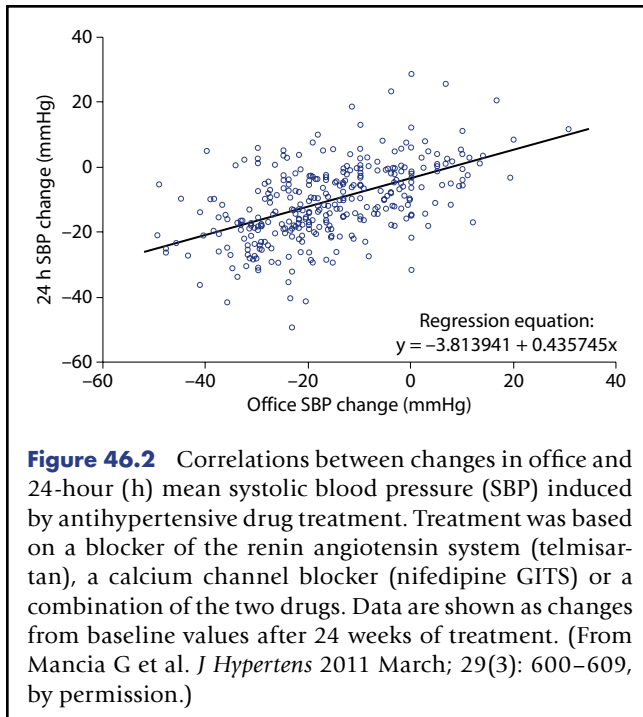
### FAILURE TO GUIDE TREATMENT BY OUT-OFFICE BP

24-h mean and home BP have a limited relationship with office BP, this being even more the case for the office and out-of-office BP changes induced by treatment (29–31). An example is given in Figure 46.2 which shows that in a large number of hypertensive patients the 24-h mean and office systolic BP changes induced by treatment exhibited a correlation coefficient of 0.43, a value compatible with marked difference between these two sets of values (31). Because ambulatory and, to a lesser extent, home BP have a steeper and closer relationship with CV events and mortality than office BP (32), the possibility exists that founding treatment on out-of-office or combined in- and out-of-office BP, rather than office BP alone, lead to a greater reduction of CV events and mortality, with thus a greater protection and a lower residual risk of the treated hypertensive individuals. At present, however, this has never been tested by an appropriate trial, and evidence is also not available on a number of important related issues. It is not known, for example, whether addition of out-of-office to office BP substantially improves

**Table 46.1** Factors possibly involved in the high residual CV risk of treated hypertensive patients

- Genetic profile
- Poor control of associated metabolic risk factors
- Suboptimal BP targets
- Failure to guide treatment by out-of-office BP
- Inadequate control of short- and long-term (visit-to-visit) BP variability
- Late initiation of antihypertensive treatment





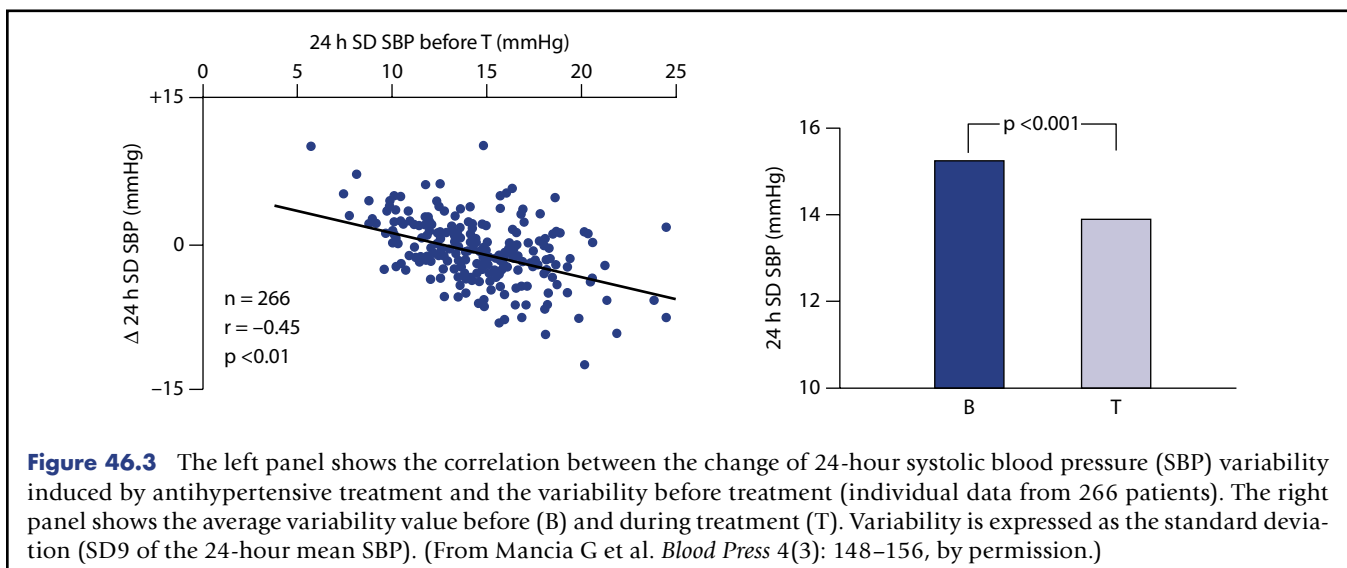
quantification of total CV risk compared to use of office BP alone (33,34), making an outcome-based trial on combined office and out-of-office-based treatment worthwhile. It is also not known which are the optimal 24-h or home BP targets because no trial has ever used ambulatory or home BP reduction to determine the effect of antihypertensive treatment on CV outcomes. It has been repeatedly reported, however, that in untreated individuals the difference between office and out-of-office BP becomes progressively less as office BP diminishes (35) and that the two average values meet around 120/70 mmHg, this being the case also in treated patients (30). If, in order to reduce residual risk, a lower office BP target will be adopted it may be justified to assume that similar values might apply to ambulatory BP as well.

## INADEQUATE CONTROL OF BP VARIABILITY

BP is highly variable within the 24 hours because of a marked difference between higher daytime and lower nighttime BP values, but also because of frequent short-lasting BP peaks and falls, particularly during the daytime (36). Evidence has been obtained that (i) short-lasting BP variations adversely affect the CV system; that is, that they increase the risk of CV events, independently of the 24-h mean BP values (36,37); (ii) compared to normotensive subjects, untreated hypertensive patients have a greater short-term BP variability, as quantified by the standard deviation of the mean 24-h daytime BP values (36,38); and (iii) the BP standard deviation is reduced by antihypertensive drugs, usually in parallel with a reduction in 24-h mean BP (36), the effect being, however, variable between patients, in part in relation to the extent of the variability before treatment (Figure 46.3) (39). It is thus possible that in some individuals an insufficient reduction in the extent of the short-term BP variations plays a role in the determination of the residual risk, although, in absence of studies on whether a treatment-induced reduction of 24-h BP variability has a protective effect independently of or additional to the reduction of 24-h mean values, this is thus far devoid of even preliminary evidence.

In contrast to the adverse prognostic role of the short-lasting BP variations, the day-night BP changes have been shown to have a protective effect, leading to an increase of CV risk as the magnitude of nocturnal hypotension decreases (32). It is not clear whether the extent of nocturnal hypotension can be altered by antihypertensive drugs, or, as for short-lasting BP variations, whether its modification can have a prognostic effect independently of and additional to the treatment-induced reduction of 24-h mean BP.

In recent years attention has been directed to another type of BP variability; that is, the BP differences that may exist between one visit and another in treated hypertensive patients. This was described in 2010 by Rothwell and co-workers (40), who reported that in the ASCOT trial greater visit-to-visit BP variations around the mean on-treatment



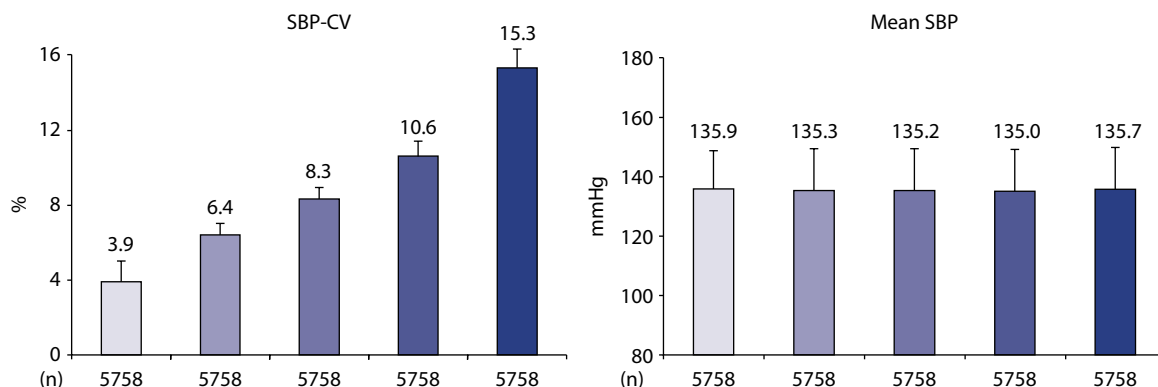


**Figure 46.4** The left panel shows the quintiles of visit-to-visit SBP variability in the patients of the ONTARGET and TRANSCEND trials. The right panel shows the corresponding mean SBP values. Variability was measured as the coefficient of variation of mean on-treatment SBP as obtained from five visits spaced by several month interval. Symbols as in the preceding figures. (From Mancia G et al. *Hypertension* 2017 November; 70(5): 938–948, by permission.)

value were associated with a greater incidence and risk of CV outcomes. It has since been shown by a large number of other trial or cohort analyses, which have further reported greater visit-to-visit BP variability values to adversely affect renal and other (e.g. cognitive function) outcomes as well (36,41). It should be emphasized that these data suffer from their post hoc nature, and thus by their comparisons of groups that differ at baseline for several variables as well as for their overall CV risk. They are also limited by the frequent quantification of BP variability by the standard deviation, a measure notoriously not independent on the mean BP value (42). However, in a few studies the adverse prognostic role of visit-to-visit BP variability has been confirmed by variability measures independent on the mean (36,41) and even documented, particularly for the lethal events, by comparison of groups with similar on-treatment

mean BP values (Figure 46.4) (42). Furthermore, and most importantly, evidence has been obtained that visit-to-visit BP variability adds its prognostic role to the one of mean on-treatment BP, a combined use of reduction in both BP mean and BP variability reflecting a greater CV risk reduction (Figure 46.5) (42). Finally, post hoc analysis of large clinical trials has shown that the risk of CV outcomes decreases progressively as the number of visits in which office BP is found to be controlled increases, independently of the mean BP value achieved over the years of treatment (Figure 46.6) (43–45). This provides clear support to the hypothesis that temporal inconsistency of chronic BP control by treatment also represents a determinant of the residual risk of treated hypertensive patients, and that its minimization by more effective long-term treatment strategies should thus be pursued. Indeed,

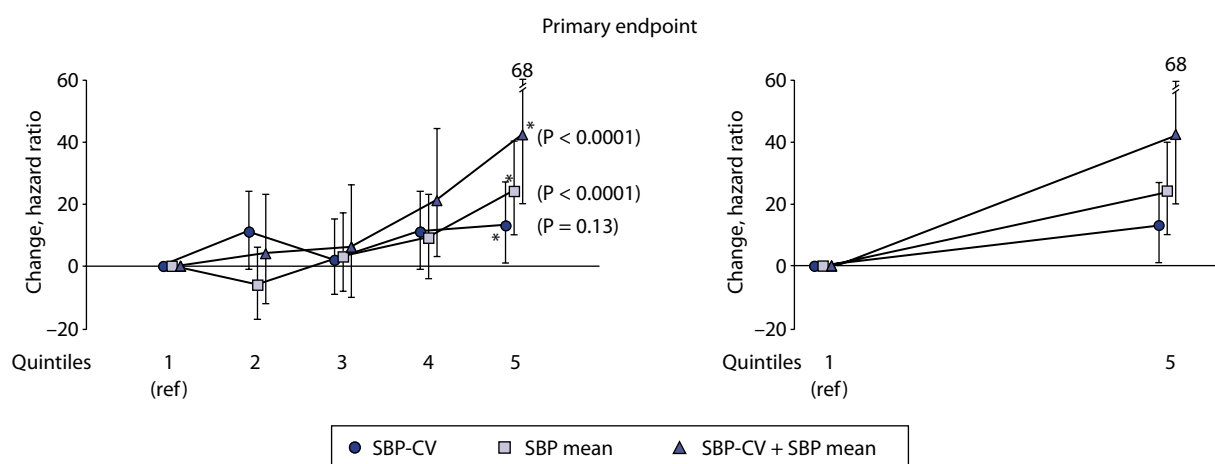


**Figure 46.5** The left panel shows the hazard ratio for cardiovascular morbidity and mortality (primary endpoint of the ONTARGET and TRANSCEND trials) data for quintiles of on-treatment visit-to-visit SBP variability (SBP-CV), on-treatment SBP mean and the two sets of quintiles combined in patients of Figure 46.4. The right panel shows the difference in the hazard ratio between quintile 5 and 1 for the above three sets of data. Quintiles 1 and 5 represent the lowest and highest values, respectively. Symbols as in preceding figures. (From Mancia G et al. *Hypertension* 2017 November; 70(5): 938–948, by permission.)

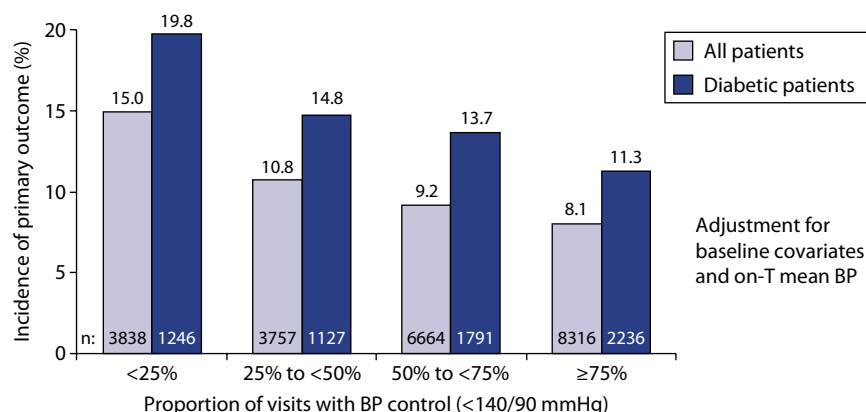


**Figure 46.6** Relationship between the percentage of visits in which blood pressure (BP) was reduced to <140/90 mmHg and the incidence of the primary endpoint (cardiovascular morbidity and mortality) in patients of the INVEST trial. Data from the whole trial population and for its diabetic fraction. Data were adjusted for the mean BP systolic and diastolic value during the treatment (T) period. (From Mancia G et al. *Hypertension* 2007; 50(2): 299–305, by permission.)

this can represent a particularly important factor to consider because in the ELSA trial the percentage of treated hypertensive patients showing BP control (reduction to <140/90 mmHg) throughout the entire treatment period (4 years) was no more than one-third of those showing the same reduction at a visit performed at the first, second, third and fourth year of treatment (46). This was the case also for ambulatory BP control (Figure 46.7), indicating that in hypertension inconsistency of temporal BP control by treatment has major dimensions.

### LATE INITIATION OF ANTIHYPERTENSIVE TREATMENT

Antihypertensive treatment has been shown to reduce CV outcomes also in severe hypertension and at a very elderly age (4). Yet, it is generally agreed that the functional and structural alterations associated with a high BP state are more effectively reversible in their early than in their later phase, when they may become scarcely

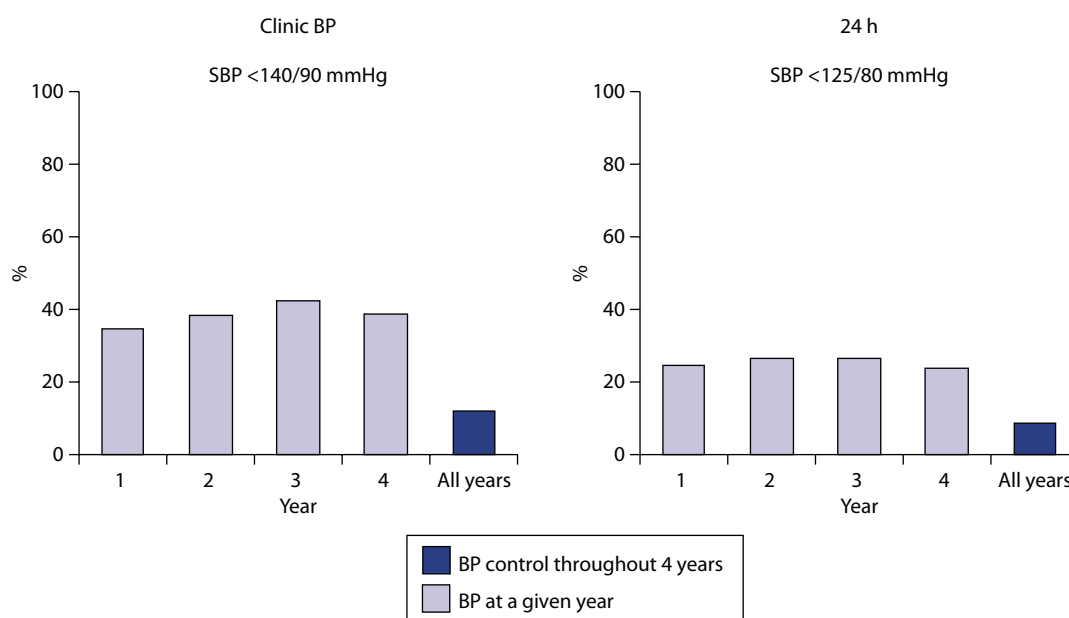


**Figure 46.7** Percentage of hypertensive patients of the ELSA study in whom treatment achieved control of office (clinic) BP (<140/90 mmHg) or 24-hour mean BP (<125/80 mmHg). Control is shown for any given year of treatment and for patients in whom it was achieved in all 4 years. Symbols as in preceding figures. (From Mancia G et al. *J Hypertens* 2007 May; 25(5): 1087–1094, by permission.)

modifiable or even unmodifiable by treatment, with an increase in the residual risk. One example is the different prevalence of echocardiographic left ventricular hypertrophy in the normotensives, treated uncontrolled and treated controlled hypertensive patients of the PAMELA population (47). In treated uncontrolled hypertensive patients, left ventricular hypertrophy was more common than in hypertensive patients in whom BP was controlled, in whom, however, prevalence was much higher than in normotensive individuals despite extension of BP control to either office and out-of-office BP (Figure 46.8). The consequences for CV events are clearly described by the old HDFP trial (48) in which antihypertensive treatment reduced CV events to a similar or even greater degree in patients at relatively high risk than in those at relatively low CV risk, the residual risk remaining, however, much higher in the former as compared to the latter condition. This points to the partial irreversibility of organ damage as well as to the incomplete ability of antihypertensive treatment to protect against hypertension-dependent events if BP-lowering interventions are delayed. This has recently received an elegant demonstration by a meta-analysis of the antihypertensive treatment trials according to the baseline CV risk level. Antihypertensive treatment was accompanied by a progressively greater reduction in the number of events from the low to the very high level of CV risk. This was paralleled, however, by a marked progressive increase in the magnitude of residual risk which exhibited a disproportionally higher value in patients in whom the baseline risk was very high versus those in which it was low (49). A time factor may thus be crucially important to limit residual risk, favouring early treatment when CV risk is still low and organ damage initial or absent.

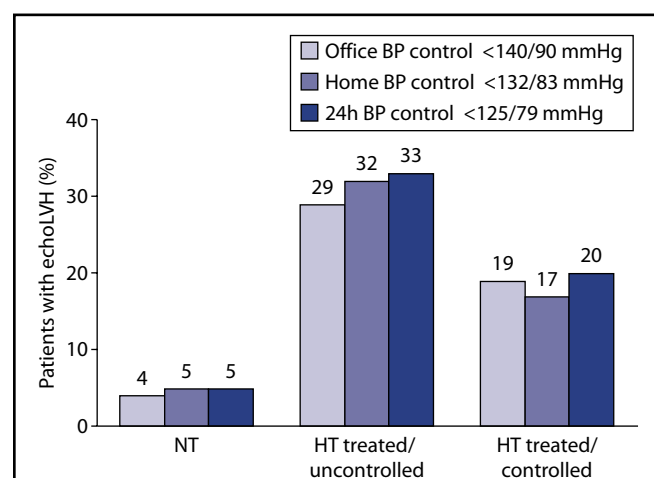


**Figure 46.8** Prevalence of echocardiographic left ventricular hypertrophy (LVH) in untreated hypertensive, treated hypertensive with control of office blood pressure (BP), home BP or 24-h mean BP, and normotensive individuals. Abbreviations: HT, hypertensive; NT, normotensive. Data from the PAMELA population. (From Mancia G et al. *Hypertension* 2002 March 1; 39(3): 744–749, by permission.)

## CONCLUSIONS

Despite years of research and improvement of the efficacy and tolerability of available antihypertensive agents and treatment strategies, hypertensive patients usually exhibit a CV risk higher than controls, even when BP is reduced to the target values believed to maximize the protective effect of antihypertensive treatment. The possibility exists that in hypertensive patients a fraction of the overall risk is genetically determined and irreversible. The residual risk, however, may also be determined by factors that are modifiable by treatment and thus potentially capable of improving the benefit of treatment and reducing residual risk.

## REFERENCES

- Andersson OK, Almgren T, Persson B et al. Survival in treated hypertension: Follow up study after two decades. *BMJ* 1998 July 18; 317(7152): 167–171.
- Isles CG, Walker LM, Beevers GD et al. Mortality in patients of the Glasgow Blood Pressure Clinic. *J Hypertens* 1986 April; 4(2): 141–156.
- Zanchetti A. Bottom blood pressure or bottom cardiovascular risk? How far can cardiovascular risk be reduced? *J Hypertens* 2009 August; 27(8): 1509–1520.
- Mancia G, Fagard R, Narkiewicz K et al. The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2013 ESH/ESC Guidelines for the management of arterial hypertension. *J Hypertens* 2013; 31: 1281–1357.
- Kannel WB. Risk stratification in hypertension: New insights from the Framingham Study. *Am J Hypertens* 2000 January; 13(12): 3S–10S.
- Grassi G, Cifkova R, Laurent S et al. Blood pressure control and cardiovascular risk profile in hypertensive patients from central and eastern European countries: Results of the BP-CARE study. *Eur Heart J* 2011 January; 32(2): 218–225.
- Muntner P, He J, Roccella EJ, Whelton PK. The impact of JNC-VI guidelines on treatment recommendations in the US population. *Hypertension* 2002 April; 39(4): 897–902.
- Yusuf S, Hawken S, Ounpuu S et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet* 2004 September 1–17; 364(9438): 937–952.
- Thomas F, Rudnicki A, Bacri AM et al. Cardiovascular mortality in hypertensive men according to presence of associated risk factors. *Hypertension* 2001 May; 37(5): 1256–1261.
- Mancia G. The association between diabetes and hypertension: An overview of its clinical impact. *Dialog Cardiovasc Med* 2016; 21(2): 91–109.
- Borghi C, Veronesi M, Bacchelli S et al. Serum cholesterol levels, blood pressure response to stress and incidence of stable hypertension in young subjects with high normal blood pressure. *J Hypertens* 2004 February; 22(2): 265–272.
- Mancia G, Facchetti R, Bombelli M et al. Relationship of office, home, and ambulatory blood pressure to blood glucose and lipid variables in the PAMELA population. *Hypertension* 2005 June; 45(6): 1072–1077.
- Bhatt DL, Steg PG, Ohman EM et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006 January 11; 295(2): 180–189.
- Ford ES, Mokdad AH, Giles WH, Mensah GA. Serum total cholesterol concentrations and awareness, treatment, and control of hypercholesterolemia among US adults: Findings from the National Health and Nutrition Examination Survey, 1999 to 2000. *Circulation* 2003 May 6; 107(17): 2185–2189.
- Chapman RH, Benner JS, Petrilla AA et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med* 2005 May 23; 165(10): 1147–1152.
- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. *Lancet* 2002 July 6; 360(9326): 7–22.

17. Sever PS, Dahlöf B, Poulter NR et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): A multicentre randomised controlled trial. *Lancet* 2003 April 5; 361(9364): 1149–1158.
18. Zanchetti A, Thomopoulos C, Parati G. Randomized controlled trials of blood pressure lowering in hypertension: A critical reappraisal. *Circ Res* 2015 March 13; 116(6): 1058–1073.
19. Ettehad D, Emdin CA, Kiran A et al. Blood pressure lowering for prevention of cardiovascular disease and death: A systematic review and meta-analysis. *Lancet* 2016 March 5; 387(10022): 957–967.
20. SPRINT Research Group, Wright JT Jr, Williamson JD et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015 November 26; 373(22): 2103–2116.
21. Vidal-Petiot E, Ford I, Greenlaw N et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: An international cohort study. *Lancet* 2016 October 29; 388(10056): 2142–2152.
22. Mancia G, Grassi G. Blood pressure targets in type 2 diabetes. Evidence against or in favour of an aggressive approach. *Diabetologia* 2018; 61(3): 517–525.
23. ACCORD Study Group, Cushman WC, Evans GW et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010 April 29; 362(17): 1575–1585.
24. Foster MC, Hwang SJ, Larson MG et al. Cross-classification of microalbuminuria and reduced glomerular filtration rate: Associations between cardiovascular disease risk factors and clinical outcomes. *Arch Intern Med* 2007 July 9; 167(13): 1386–1392.
25. Corrao G, Mazzola P, Monzio Compagnoni M et al. Antihypertensive medications, loop diuretics, and risk of hip fracture in the elderly: A Population-Based Cohort Study of 81,617 Italian Patients Newly Treated Between 2005 and 2009. *Drugs Aging* 2015 November; 32(11): 927–936.
26. Ambrosioni E, Leonetti G, Pessina AC et al. Patterns of hypertension management in Italy: Results of a pharmacoepidemiological survey on antihypertensive therapy. Scientific Committee of the Italian Pharmacoepidemiological Survey on Antihypertensive Therapy. *J Hypertens* 2000 November; 18(11): 1691–1699.
27. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment in hypertension: 9. Discontinuations for adverse events attributed to different classes of antihypertensive drugs: Meta-analyses of randomized trials. *J Hypertens* 2016 October; 34(10): 1921–1932.
28. Hirakawa Y, Arima H, Webster R et al. Risks associated with permanent discontinuation of blood pressure-lowering medications in patients with type 2 diabetes. *J Hypertens* 2016 April; 34(4): 781–787.
29. Mancia G, Coca A, Chazova I et al. Effects on office and home blood pressure of the lercanidipine-enalapril combination in patients with Stage 2 hypertension: A European randomized, controlled clinical trial. *J Hypertens* 2014 August; 32(8): 1700–1707.
30. Mancia G, Parati G, Bilo G et al. Ambulatory blood pressure values in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET). *Hypertension* 2012 December; 60(6): 1400–1406.
31. Mancia G, Parati G, Bilo G et al. Blood pressure control by the nifedipine GITS-telmisartan combination in patients at high cardiovascular risk: The TALENT study. *J Hypertens* 2011 March; 29(3): 600–609.
32. Mancia G, Verdecchia P. Clinical value of ambulatory blood pressure: Evidence and limits. *Circ Res* 2015 March 13; 116(6): 1034–1045.
33. Zanchetti A, Mancia G. Longing for clinical excellence: A critical outlook into the NICE recommendations on hypertension management—is nice always good? *J Hypertens* 2012 April; 30(4): 660–668.
34. Mortensen RN, Gerds TA, Jeppesen JL, Torp-Pedersen C. Office blood pressure or ambulatory blood pressure for the prediction of cardiovascular events. *Eur Heart J* 2017 November 21; 38(44): 3296–3304.
35. Segà R, Cesana G, Milesi C et al. Ambulatory and home blood pressure normality in the elderly: Data from the PAMELA population. *Hypertension* 1997 July; 30: 1–6.
36. Mancia G. Short- and long-term blood pressure variability: Present and future. *Hypertension* 2012 August; 60(2): 512–517.
37. Mancia G, Bombelli M, Facchetti R et al. Long-term prognostic value of blood pressure variability in the general population: Results of the Pressioni Arteriose Monitorate e Loro Associazioni Study. *Hypertension* 2007 June; 49(6): 1265–1270.
38. Mancia G, Ferrari A, Gregorini L et al. Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. *Circ Res* 1983 July; 53(1): 96–104.
39. Mancia G, Omboni S, Ravogli A et al. Ambulatory blood pressure monitoring in the evaluation of antihypertensive treatment: Additional information from a large data base. *Blood Press* 1995 May; 4(3): 148–156.
40. Rothwell PM, Howard SC, Dolan E et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 2010 March 13; 375(9718): 895–905.
41. Stevens SL, Wood S, Koshiaviv C et al. Blood pressure variability and cardiovascular disease. A systematic review and meta-analysis. *BMJ* 2016; 354: i4098.
42. Mancia G, Schumacher H, Böhm M et al. Relative and Combined prognostic importance of on-treatment mean and visit-to-visit blood pressure variability in ONTARGET and TRANSCEND patients. *Hypertension* 2017 November; 70(5): 938–948.
43. Mancia G, Messerli F, Bakris G et al. Blood pressure control and improved cardiovascular outcomes in the International Verapamil SR-Trandolapril Study. *Hypertension*. 2007 August; 50(2): 299–305.
44. Mancia G, Schumacher H, Redon J et al. Blood pressure targets recommended by guidelines and incidence of cardiovascular and renal events in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET). *Circulation* 2011 October 18; 124(16): 1727–1736.
45. Mancia G, Kjeldsen SE, Zappe DH et al. Cardiovascular outcomes at different on-treatment blood pressures in the hypertensive patients of the VALUE trial. *Eur Heart J* 2016 March 21; 37(12): 955–964.
46. Mancia G, Parati G, Bilo G et al. Assessment of long-term antihypertensive treatment by clinic and ambulatory blood pressure: Data from the European Lacidipine Study on Atherosclerosis. *J Hypertens* 2007 May; 25(5): 1087–1094.
47. Mancia G, Carugo S, Grassi G et al. Prevalence of left ventricular hypertrophy in hypertensive patients without and with blood pressure control: Data from the PAMELA population. Pressioni Arteriose Monitorate e Loro Associazioni. *Hypertension* 2002 March 1; 39(3): 744–749.
48. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the hypertension detection and follow-up program. III. Reduction in stroke incidence among persons with high blood pressure. *JAMA* 1982 February 5; 247(5): 633–638.
49. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 3. Effects in patients at different levels of cardiovascular risk—overview and meta-analyses of randomized trials. *J Hypertens* 2014 December; 32(12): 2305–2314.





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# Section VIII

## Special Conditions

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# ETHNIC FACTORS IN HYPERTENSION

# 47

*Katarzyna Stolarz-Skrzypek, Danuta Czarnecka and  
Andrzej Januszewicz*

## INTRODUCTION

The increasing ethnic diversity of the European and extra-European populations will challenge the abilities of medical professionals to deal with diseases specific for particular ethnicities but also, more importantly, with highly prevalent chronic morbid conditions that might differ by presentation in different ethnic groups.

Ethnicity has been reported to influence prevalence of hypertension, cardiovascular (CV) risk and hypertension-related organ damage. Ethnic groups differ with regard to pathogenesis of hypertension, which might translate into different optimal antihypertensive treatment options.

## EPIDEMIOLOGY OF HYPERTENSION

Hypertension prevalence varies around the world. Over the past decade, prevalence has increased in economically developing countries and has remained stable or decreased in economically developed countries (1). According to an analysis of worldwide data, the region with the highest hypertension prevalence is 'Latin America and the Caribbean' (i.e. Mexico, Paraguay, Venezuela) for men (44.5%) and the 'former socialist economies' (i.e. Slovakia) for women (45.9%) (1). The lowest estimated prevalence for both men (17%) and women (14.5%) is in the region 'other Asia and islands' (i.e. Korea, Thailand, Taiwan) (1).

Published data show that the prevalence of hypertension and the rate of blood pressure (BP)-related complications are substantially higher among blacks than they are among whites (2), yet most available studies contrasted blacks from African ancestry with whites in the United States. Recently in the multi-ethnic population study, reported prevalence of hypertension on conventional BP measurement amounted to 13.3% and 28.9%, respectively, among South Africans and Flemish whites and to 34.1% among black South Africans (3). On the other hand, in another multicentre study, prevalence of masked hypertension, irrespective of treatment status, was similar among black Nigerians and Japanese and white people of the reference group (4).

Recent estimates of between-ethnicity differences have been provided also from Europe. Modesti et al. (5) performed a systematic review and meta-analysis of observational studies conducted in Europe that examined BP in non-selected adult subjects of sub-Saharan African, South Asian and European origin. Compared with Europeans, sub-Saharan Africans had higher values of both systolic and diastolic BP. South Asians had lower systolic BP than Europeans, but similar diastolic BP values (5).

Bosu et al. (6) systematically reviewed data on hypertension prevalence among West Africa's workforce. Generally, the prevalence was high, and in 40 studies with a common definition of hypertension the prevalence ranged from 12.0% among automobile garage workers to 68.9% among traditional chiefs. A significant proportion of patients were undiagnosed, severe or complicated (6).

Asians represent the largest racial group in the world. The prevalence of hypertension in China, the most populated country in the world, has increased rapidly over the past decade, from approximately 20% in 2000 to over 30%, based on more recent estimates (7).

These cross-sectional observations translate into lifetime risk of hypertension. In MESA (Multi-Ethnic Study of Atherosclerosis), the percentage of the population developing hypertension was higher for African Americans and Hispanics than for whites and Asians (10,11). For adults 45 years of age without hypertension at baseline, the 40-year risk of developing hypertension was estimated as 93% for African American, 92% for Hispanic, 86% for white, and 84% for Chinese adults (8).

Moreover, ethnicity is also an important risk factor for uncontrolled hypertension. In the United States, hypertension control rates are lower for blacks, Hispanic Americans, and Asian Americans than for whites (10). Among men with hypertension, non-Hispanic white (53.8%) adults had a higher prevalence of controlled high BP than did non-Hispanic black (43.8%), non-Hispanic Asian (39.9%) and Hispanic (43.5%) adults. For women with hypertension, the percentage of non-Hispanic white (59.1%) adults with controlled high BP was higher than among non-Hispanic black (52.3%) and non-Hispanic Asian (46.8%) adults (10).

In Hispanic Americans, the lower control rates result primarily from lack of awareness and treatment (11), whereas in blacks, awareness and treatment are at least as high as in whites, but hypertension is more severe, and some agents are less effective at BP control (9).

Furthermore, treatment-resistant hypertension is more prevalent in adults of African descent in the United States than in other ethnicity groups (12).

Ethnicities differ significantly also in terms of other cardiovascular risk factor prevalence. African Americans have a high prevalence of obesity, diabetes and hypercholesterolemia (13). In Mexican American men and women, high rates of obesity (36.5 and 42.6%, respectively) and hypercholesterolaemia (51.7 and 36.9%) were noted (14). As seen in blacks and Hispanics, hypertension is often present with other comorbid conditions in the Asian patients. Diabetes, in particular, occurs often in the Asian population, and develops at an earlier age relative to Europeans (15).

## **PATHOPHYSIOLOGIC CONSIDERATIONS**

African Americans do have a greater increase in BP for a given exposure to dietary sodium and have a greater frequency of salt sensitivity compared with European Americans. The Dietary Approaches to Stop Hypertension (DASH)-sodium diet trial (16) was designed to determine whether or not sodium reduction would further improve the BP reduction achieved with the DASH diet. The greatest benefit was seen in the African American hypertensive participants consuming the 1500-mg per day DASH-sodium diet. In this group, systolic BP was lowered by 12.6 mmHg compared with 9.5 mmHg in the European American hypertensive participants on the same diet (16).

Obesity contributes significantly to hypertension risk in all populations, particularly racial and ethnic minorities (9). The excess prevalence of salt sensitivity among African Americans relates to the increased frequency of obesity in this population. It has been demonstrated in both Caucasians and African Americans that obesity is linked to salt sensitivity. Low dietary potassium intake contributes to salt sensitivity, as high levels of potassium intake diminish the pressor effect of salt in salt-sensitive African Americans (17).

Data demonstrating lower prevalence of hypertension among populations of African descent from the Caribbean and rural continental Africa relative to those in the United States (18) support the hypothesis that environmental factors play an important role in the development of hypertension in blacks living in the United States. In a standardized evaluation of populations in West Africa (Nigeria and rural and urban Cameroon), the Caribbean (Jamaica, St. Lucia and Barbados), and the United States (Chicago), the hypertension rate was directly related to increasing Westernization, with increasing prevalence from rural Cameroon (15.4%) to urban Cameroon (19.1%) to the United States (32.6%); regression analysis found that 70% of the geographic variation in hypertension prevalence was attributable to two characteristics, body mass index (BMI) and the sodium:potassium ratio (18).

In African Americans, low-renin, salt-sensitive hypertension may be genetically based (19). Plasma renin activity (PRA) and aldosterone in 1021 participants in the

MESA not currently taking antihypertensives showed, that compared with whites, blacks had 28% lower PRA and 17.4% lower aldosterone (20).

Recent data point to a central role for the balance between nitric oxide (NO) bioavailability and creatinine kinase (CK) activity (21). The NO and CK systems share a common precursor in L-arginine and display antagonizing effects with mutual inhibition. NO inhibits CK, lowers BP and promotes cardiovascular health (21). High CK activity is thought to promote salt retention and vascular contractility, with low renin as an epiphenomenon. Patients of African ancestry are reported to have low NO bioavailability (22), high CK activity (21) and low L-arginine (23), with restored NO bioavailability upon L-arginine supplementation (24).

The prevalence of risk factors for hypertension may also differ between ethnic groups within the same race. In the European Project on Genes in Hypertension (EPOGH), white Europeans from six centres located in different countries had divergent characteristics in terms of lifestyle factors, i.e. dietary sodium intake or alcohol consumption (25,26). The EPOGH demonstrated that phenotype-genotype associations strongly depend on host factors such as gender, but also lifestyle, in particular salt intake as reflected by the 24-h urinary excretion of sodium, that is at least partially determined by the ethnicity (27,28) and may translate into divergent BP levels and BP-related target-organ damage (29,30).

## **END-ORGAN DAMAGE AND CLINICAL COMPLICATIONS**

Cross-sectional studies (31) have documented that blacks have a steeper increase in left ventricular mass with each unit of increase in BP as compared to whites.

These effects may also be observed when indices of left ventricular hypertrophy are assessed based on ECG recording. Odili et al. (32) analysed blacks from sub-Saharan Africa and Flemish whites. In both ethnicities, the precordial QRS voltage sums, combined or not with the limb voltages, and the voltage-duration products were positively associated with both office and home systolic BP; however, the slopes of these associations were up to three times steeper in blacks than in whites.

The current state of knowledge indicates that the prevalence of left ventricular remodelling or hypertrophy is not only higher (33) but also has more deleterious effects (34) among blacks.

Morbidity and mortality attributed to hypertension are also more common in blacks and Hispanic Americans than in whites. Blacks have 1.3-times greater risk of nonfatal stroke, 1.8-times greater risk of fatal strokes, 1.5-times greater risk of heart failure (HF), and 4.2-times greater risk of end-stage renal disease (ESRD) (35). Studies have shown that Hispanic Americans also have an increased cardiovascular risk compared with non-Hispanic whites (11).

The four to five times greater risk for developing chronic kidney disease (CKD) or ESRD in hypertensive blacks has been linked to unique genetic polymorphisms, including MYH9 and apolipoprotein L1 gene (APOL1), which is found primarily with African ancestry and associated with focal segmental glomerular sclerosis and hypertensive kidney disease (36).



Early hypertension onset and premature CV disease in blacks may be related to blunted nocturnal BP declines, starting in childhood and exacerbated with age (36,37). Wang et al. recently reported ethnic differences in the longitudinal effect of ambulatory BP measured multiple times in youth and young adults over a 15-year period. Beginning at adolescence, African Americans had higher systolic and diastolic BP at night and during the day compared with European Americans. African Americans had a more rapid increase in systolic BP with ageing and a significantly greater nocturnal BP compared with European Americans. Importantly, non-dipping of nocturnal BP began very early, at 10 years of age (36,37).

## ANTIHYPERTENSIVE TREATMENT

### LIFESTYLE CHANGES

Lifestyle modification (i.e. weight reduction, dietary modification and increased physical activity) is particularly important in blacks and Hispanic Americans for prevention and first-line or adjunctive therapy of hypertension. However, the adoption of lifestyle recommendations is often challenging in ethnic minority patients because of poor social support, limited access to exercise opportunities and healthy foods, and financial considerations (9).

High BMI, especially abdominal obesity, may explain much of the variation of hypertension and CV disease among groups. In a retrospective study of 150,753 California adults, Asians had the lowest BMI among all groups, but the impact of increasing BMI on the risk of hypertension and diabetes was significantly greater in Asians; for each one unit increase in BMI, Asians were significantly more likely to have hypertension (OR 1.15; 95% CI 1.13–1.18) compared to non-Hispanic whites, blacks, and Hispanics (38).

Especially in blacks, there is strong evidence for the DASH diet (high in fresh fruits and vegetables and low-fat dairy products) (39), Mediterranean eating patterns, and sodium restriction (40).

### PHARMACOTHERAPY

In black hypertensive patients, compared with hypertension in other ethnicities, the disorder is often more severe, more resistant to treatment, and leads to earlier end-organ damage and premature death, as described above. Thus, hypertension seems to be a more aggressive disease in patients of African ancestry. This has important implications for the choice of an antihypertensive agent.

In blacks, thiazide-type diuretics and calcium channel blockers are more effective in lowering BP when given as monotherapy or as initial agents in multidrug regimens (41). In addition, thiazide-type agents are superior to drugs that inhibit the renin-angiotensin system (i.e. angiotensin converting enzyme [ACE] inhibitors, angiotensin-receptor blockers [ARBs], renin inhibitors, and beta-blockers) for prevention of selected clinical outcomes in blacks (42). The calcium antagonist amlodipine is as effective as chlorthalidone and more effective than the ACE inhibitor lisinopril in reducing BP, CV disease and stroke events but less effective

in preventing heart failure (43). Blacks have a greater risk of angioedema with ACE inhibitors (43), and Asian Americans have a higher incidence of ACE inhibitor – induced cough (44). ACE inhibitors and ARBs are recommended more generally as components of multidrug antihypertensive regimens in blacks with CKD (9), with the addition of beta-blockers in those with heart failure (9). Beta-blockers are recommended for treatment of patients with coronary heart disease who have had a myocardial infarction. Most patients with hypertension, especially blacks, require  $\geq 2$  antihypertensive medications to achieve adequate BP control. A single-tablet combination that includes either a diuretic or a calcium antagonist may be particularly effective in achieving BP control in blacks. Racial and ethnic differences should not be the basis for excluding any class of antihypertensive agent in combination therapy (9).

Patients of African ancestry as a group respond better to calcium blockers and diuretics, while the response to beta-adrenergic blockade and inhibition of the ACE is attenuated (45). Brewster and colleagues systematically reviewed the international contemporary literature on pharmacotherapy in persons of African ancestry and concluded the response was superior in blacks for thiazide-like diuretics and calcium channel blockers, as compared to beta-adrenergic blockers and ACE inhibitors/ARBs. Overall, as compared to genetic markers, self-defined ancestry appeared to be the best predictor of individual responses to antihypertensive drugs (46). Nevertheless, the same authors recently cautioned that there was also a large degree of overlap in BP lowering between blacks and whites, providing caution for making therapeutic decisions based solely upon ethnicity (race) (47).

Brewster et al. in their systematic review searched for the explanation of the differential clinical efficacy of antihypertensive drugs in patients of African ancestry. Pharmacokinetics, plasma renin and genetic polymorphisms did not well predict the response of patients of African ancestry to antihypertensive drugs. The magnitude of the effects of variation in single-candidate genes on antihypertensive drug responses appeared to be very modest, accounting for only a small percentage of total variation in response. No unique mutation was by itself predictive of the therapeutic response to these drugs, and even the combined effects of polymorphisms did not account for enough variation in response to be clinically useful (46).

While some argue that the persistent racial and ethnic differences in hypertension control is due to less aggressive treatment in blacks, fewer or less effective medications, or genetic and other physiological factors making medications less effective for blacks than whites (47), others suggest that differences in social and healthcare environments account for substantial disparities (47). Characteristics of local environmental factors such as neighbourhood poverty, crime rates, availability of healthy foods and racial isolation contribute to disparities in BP control (47).

Health behaviours are significant contributors to hypertension disparities. Adherence to hypertension treatment recommendations is lower in black compared with white individuals (48) and dissimilarities in medication adherence are linked with hypertension control disparities (49). Prospective, longitudinal analysis of the prevalence of cardiovascular health metrics among 5310 blacks (63.5% women) from the Jackson Heart Study showed that only 19% engaged in adequate physical activity, 18% had

adequate BP, and 14% had a normal BMI. Meeting ideal dietary intakes was rare (0.9%), with extremely low prevalence of achieving sodium (0.2%) and wholegrain (4.1%) recommendations (50).

Not enough effort has been made to include Hispanic Americans in clinical studies in sufficient representative numbers. Therefore, very little evidence-based information is available in this population, and current guidelines do not provide specific guidance for treating hypertension in Hispanic patients. Given the clustering of hypertension with obesity, diabetes, and metabolic syndrome in Hispanics and the role of the renin–angiotensin system in the pathogenesis of these conditions, renin–angiotensin system inhibitors are postulated as the most suitable medications (51).

Marshall et al. (52) investigated whether patients' views with regard to antihypertensive treatment differ internationally by culture or ethnic group and whether the research could inform interventions to improve adherence. Included studies came from 16 countries. Nonadherence to hypertension treatment often resulted from patients' understanding of the causes and effects of hypertension; particularly relying on the presence of stress or symptoms to determine if BP was raised. These beliefs were remarkably similar across ethnic and geographical groups, supporting the authors' conclusion that calls for culturally specific education for individual ethnic groups may therefore not be justified (52).

## CONCLUSION

Ethnic factors play an important role in the pathogenesis of hypertension. Ethnic disparity is observed for prevalence of hypertension and other CV risk factors. Thus, treatment decisions should account also for ethnicity.

## REFERENCES

- Kearney PM, Whelton M, Reynolds K, et al. Worldwide prevalence of hypertension: A systematic review. *J Hypertens* 2004; 22(1): 11–19.
- Hara A, Thijs L, Asayama K, et al. Blood pressure in relation to environmental lead exposure in the national health and nutrition examination survey 2003 to 2010. *Hypertension* 2015; 65(1): 62–69.
- Wei FF, Drummen NEA, Schutte AE et al. Vitamin K dependent protection of renal function in multi-ethnic population studies. *EBioMedicine* 2016; 4: 162–169.
- Odili AN, Thijs L, Hara A, et al. Prevalence and determinants of masked hypertension among black Nigerians compared with a reference population. *Hypertension* 2016; 67(6): 1249–1255.
- Modesti PA, Reboldi G, Cappuccio FP, et al. Panethnic differences in blood pressure in Europe: A systematic review and meta-analysis. *PLOS ONE* 2016; 11(1): e0147601.
- Bosu WK. The prevalence, awareness, and control of hypertension among workers in West Africa: A systematic review. *Glob Health Action* 2015 Jan 22; 8: 26227.
- Li H, Meng Q, Sun X et al. Prevalence, awareness, treatment, and control of hypertension in rural China: Results from Shandong Province. *J Hypertens* 2010; 28(3): 432–438.
- Carson AP, Howard G, Burke GL, et al. Ethnic differences in hypertension incidence among middle-aged and older adults: The multi-ethnic study of atherosclerosis. *Hypertension* 2011; 57(6): 1101–1107.
- Whelton PK, Carey RM, Aronow WS et al. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017 7; 71(6): e13–e115.
- Yoon SS, Carroll MD, Fryar CD et al. Hypertension prevalence and control among adults: United States, 2011–2014. *NCHS Data Brief* 2015; (220): 1–8.
- Margolis KL, Piller LB, Ford CE, et al. Blood pressure control in Hispanics in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension* 2007; 50(5): 854–861.
- Egan BM. Treatment resistant hypertension. *Ethn Dis* 2015; 25(4): 495.
- Romero CX, Romero TE, Shlay JC et al. Changing trends in the prevalence and disparities of obesity and other cardiovascular disease risk factors in three racial/ethnic groups of USA adults. *Adv Prev Med* 2012; 2012: 172423.
- Daviglus ML, Talavera GA, Avilés-Santa ML et al. Prevalence of major cardiovascular risk factors and cardiovascular diseases among Hispanic/Latino individuals of diverse backgrounds in the United States. *JAMA* 2012; 308(17): 1775.
- Ramachandran A, Snehalatha C, Shetty AS, Nanditha A. Trends in prevalence of diabetes in Asian countries. *World J Diabetes* 2012; 3(6): 110–497.
- Sacks FM, Svetkey LPVW, et al. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. *N Engl J Med* 2001; 344(1): 3–10.
- Morris RC, Sebastian A, Forman A, et al. Normotensive salt sensitivity: Effects of race and dietary potassium. *Hypertension* 1999; 33: 18–23.
- Cooper R, Rotimi C, Ataman S, et al. The prevalence of hypertension in seven populations of West African origin. *Am J Public Health* 1997; 87(2): 160–168.
- Tu W, Pratt J. A consideration of genetic mechanisms behind the development of hypertension in blacks. *Curr Hypertens Rep* 2013; 15(2): 108–113.
- Rifkin DE, Khaki AR, Jenny NS, et al. Association of renin and aldosterone with ethnicity and blood pressure: The multi-ethnic study of atherosclerosis. *Am J Hypertens* 2014; 27(6): 801–810.
- Brewster LM, Mairuhu G, Bindraban NR, et al. Creatine kinase activity is associated with blood pressure. *Circulation* 2006; 114(19): 2034–2039.
- Kalinowski L, Dobrucki IT, Malinski T. Race-specific differences in endothelial function: Predisposition of African Americans to vascular diseases. *Circulation* 2004; 109(21): 2511–2517.
- Glyn MC, Anderssohn M, Lüneburg N, et al. Ethnicity-specific differences in L-arginine status in South African men. *J Hum Hypertens* 2012; 26(12): 737–743.
- Houghton JL, Philbin EF, Strogatz DS et al. The presence of African American race predicts improvement in coronary endothelial function after supplementary L-arginine. *J Am Coll Cardiol* 2002; 39(8): 1314–1322.
- Stolarz K, Staessen JA, Kuznetsova T et al. Host and environmental determinants of heart rate and heart rate variability in four European populations. *J Hypertens* 2003; 21(3): 525–535.
- Stolarz K, Staessen JA, Kawecka-Jaszcz K, et al. Genetic variation in CYP11B2 and AT1R influences heart rate variability conditional on sodium excretion. *Hypertension* 2004; 44(2): 156–162.
- Tikhonoff V, Kuznetsova T, Stolarz K, et al.  $\beta$ -adducin polymorphisms, blood pressure, and sodium excretion in three European populations. *Am J Hypertens* 2003; 16(10): 840–846.
- Kuznetsova T, Staessen JA, Brand E, et al. Sodium excretion as a modulator of genetic associations with cardiovascular phenotypes in the European Project on Genes in Hypertension. *J Hypertens* 2006; 24: 235–242.
- Wojciechowska W, Staessen JA, Stolarz K et al. Association of peripheral and central arterial wave reflections with the CYP11B2–344C allele and sodium excretion. *J Hypertens* 2004; 22(12): 2311–2319.
- Kuznetsova T, Staessen JA, Stolarz K et al. Relationship between left ventricular mass and the ACE D/I polymorphism varies according to sodium intake. *J Hypertens* 2004; 22(2): 287–295.
- Lorber R, Gidding SS, Daviglus ML et al. Influence of systolic blood pressure and body mass index on left ventricular structure in healthy African-American and white young adults: The CARDIA study. *J Am Coll Cardiol* 2003; 41(6): 955–960.
- Odili AN, Thijs L, Yang W-Y et al. Office and home blood pressures as determinants of electrocardiographic left ventricular hypertrophy among black Nigerians compared with white Flemish. *Am J Hypertens* 2017; 3 (11): 1083–1092.
- Rodriguez CJ, Diez-Roux AV, Moran A et al. Left ventricular mass and ventricular remodeling among Hispanic subgroups compared with non-Hispanic blacks and whites. MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2010; 55(3): 234–242.

34. East MA, Jollis JG, Nelson CL et al. The influence of left ventricular hypertrophy on survival in patients with coronary artery disease: Do race and gender matter? *J Am Coll Cardiol* 2003; 41(6): 949–954.
35. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics—2017 update. *Circulation* 2017; 135(10).
36. Tayo BO, Kramer H, Salako BL, et al. Genetic variation in APOL1 and MYH9 genes is associated with chronic kidney disease among Nigerians. *Int Urol Nephrol* 2013; 45(2): 485–494.
37. Wang X, Poole JC, Treiber FA, Harshfield GA, Hanevold CD, Snieder H. Ethnic and gender differences in ambulatory blood pressure trajectories results from a 15-year longitudinal study in youth and young adults. *Circulation* 2006; 114(25): 2780–2787.
38. Wong RJ, Chou C, Sinha SR, et al. Ethnic disparities in the association of body mass index with the risk of hypertension and diabetes. *J Community Health* 2014; 39(3): 437–445.
39. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* 1997; (4641): 1117–1124.
40. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol* 2014; 63(25 Part B): 2960–2984.
41. Wright JT. Outcomes in hypertensive black and nonblack patients treated with chlorthalidone, amlodipine, and lisinopril. *JAMA* 2005; 293(13): 1595.
42. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008; 18: 19–1527.
43. Wright JT. ALLHAT findings revisited in the context of subsequent analyses, other trials, and meta-analyses. *Arch Intern Med* 2009; 169(9): 832.
44. Woo KS, Nicholls MG. High prevalence of persistent cough with angiotensin converting enzyme inhibitors in Chinese. *Br J Clin Pharmacol* 1995; 40(2): 141–834.
45. Sehgal AR. Overlap between whites and blacks in response to antihypertensive drugs. *Hypertension* 2004; 43(3): 566–572.
46. Brewster LM, Seedat YK. Why do hypertensive patients of African ancestry respond better to calcium blockers and diuretics than to ACE inhibitors and  $\beta$ -adrenergic blockers? A systematic review. *BMC Med* 2013; 11(1): 141.
47. Seedat YK, Brewster LM. What role does African ancestry play in how hypertensive patients respond to certain antihypertensive drug therapy? *Expert Opin Pharmacother* 2014; 15(2): 159–161.
48. Kressin NR, Orner MB, Manze M, et al. Understanding contributors to racial disparities in blood pressure control. *Circ Cardiovasc Qual Outcomes* 2010; 3(2): 173–180.
49. Bosworth HB, Powers B, Grubbs JM et al. Racial differences in blood pressure control: Potential explanatory factors. *J Gen Intern Med* 2008; 23(5): 692–698.
50. Djoussé L, Petrone AB, Blackshear C, et al. Prevalence and changes over time of ideal cardiovascular health metrics among African-Americans: The Jackson Heart Study. *Prev Med* 2016; (617): 111–116.
51. Guzman NJ. Epidemiology and management of hypertension in the Hispanic population: A review of the available literature. *Am J Cardiovasc Drugs* 2012; 12(3): 165–178.
52. Marshall IJ, Wolfe CDA, McKeivitt C. Lay perspectives on hypertension and drug adherence: Systematic review of qualitative research. *BMJ* 2012; 345: e3953.



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# RESISTANT HYPERTENSION: MEDICAL TREATMENT

# 48

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## INTRODUCTION

Hypertension remains poorly controlled worldwide, and its incidence is increasing due to ageing of the population and the obesity epidemic (1,2). The blood pressure (BP) goals generally recommended for all hypertensive patients are a seated, attended office systolic BP (SBP) of less than 140 mmHg and a diastolic BP (DBP) of less than 90 mmHg. According to the 2018 joint European Society of Hypertension (ESH)–European Society of Cardiology (ESC) guidelines (3), hypertension is defined as resistant to treatment ‘when the recommended treatment strategy fails to office SBP and DBP values to below 140 mmHg and/or 90 mmHg, respectively, and the inadequate control of BP is confirmed by ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM), in patients whose adherence to therapy has been confirmed. The recommended treatment strategy should include appropriate lifestyle measures and treatment with optimal or best-tolerated doses of three or more drugs that should include a diuretic and typically an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), and a CCB [calcium channel blocker] (Class I A recommendation). Pseudo-resistant hypertension and secondary causes of hypertension should also have been excluded’ (3). Pseudo-resistant hypertension may be of various origins, including poor adherence to prescribed medications (occurring in >50% of patients), white-coat phenomenon, poor office-BP measurement technique, marked brachial artery calcification (especially in older patients) and clinician inertia (3,4). The American Heart Association guidelines also include patients with BP controlled by four or more drugs in the definition of resistant hypertension (RHTN) (5). RHTN is associated with a higher prevalence of end-organ damage, including left ventricular hypertrophy, carotid intima-media thickening, microalbuminuria and retinal lesions than well-controlled hypertension (6,7). The frequent association of target-organ damage and the clustering of cardiovascular risk factors in patients with RHTN accounts for the higher risk of a major cardiovascular event in these patients and thus a poor short-term prognosis (8).

The prevalence of true RHTN (9,10) is lower than that of ‘apparent’ RHTN, which may be due to inadequate office BP measurement, white-coat hypertension, the use of non-optimal combinations of drugs at non-adequate doses, or nonadherence to treatment. Its estimation thus depends on multiple factors, including the clinical setting (general population, tertiary referral centre, clinical trial), the time frame of evaluation, the classes and optimal doses of anti-hypertensive treatment used, the exclusion or retention of patients not complying with treatment, the method of BP measurement and the BP threshold selected. A meta-analysis of 20 observational studies and randomized controlled trials estimated the prevalence of RHTN at 13.7% (95% confidence interval [CI]: 11.2–16.22%) for the observational studies and 16.3% (95% CI: 10.7–21.9%) for the randomized controlled trials (10). Prevalence of RHTN in the UK declined from 2004, reaching 6.5% of the hypertensive population in 2015 (11). Finally, the prevalence of RHTN is highest in patients with a low glomerular filtration rate (GFR) and albuminuria (i.e. chronic kidney disease), in which it may be as high as 50% (12). In all these settings, the prevalence of RHTN is probably overestimated because it is generally defined on the basis of office BP measurements. The systematic use of ABPM in a Spanish registry showed that 37.5% of patients actually had pseudoresistant HTN (13). ABPM or self-BP measurement at home should thus be used systematically for the definition and confirmation of RHTN, to exclude pseudoresistance (4,5,14,15).

## MEDICAL TREATMENT FOR PATIENTS WITH RHTN

Multidrug regimens are required to achieve BP goals through interference with the complex interplay of different pathways implicated in the pathogenesis of RHTN, which by contributing to volume and sodium overload increases arterial stiffness, and renal fibrosis in the mid- and long-term. Other factors including age, ethnicity, the presence of associated comorbid conditions, chronic kidney disease and proteinuria, compelling indications for certain classes



of drugs, and the risk of drug–drug interactions should be taken into account for the treatment (5,14,15).

## LIFESTYLE CHANGES

Reduction of sodium and alcohol intake, as well as weight reduction and regular exercise should always be part of the treatment approach (3,5,14,15). Excessive salt consumption decreases the effectiveness of diuretics and renin-angiotensin system (RAS) blockers (16,17), especially in elderly patients, in those of African origin and in those with chronic kidney disease. Daily salt intake should be evaluated by measuring sodium excretion over a 24-h period. Alcohol abuse is also a major factor contributing to poor BP control (17). Overweight and obesity are frequently observed in patients with RHTN (18). Obstructive sleep apnoea (OSA) is almost four times more frequent in patients with RHTN than in patients with controlled hypertension (19). For those with OSA, continuous positive airway pressure (CPAP) may be of moderate benefit (20), but this remains a matter of debate for patients with RHTN (21,22), and long-term compliance with CPAP may be problematic (23). Mandibular advancement devices have also been shown to reduce BP (24). However, it remains unclear whether patients remain sufficiently adherent to lifestyle changes in the long term.

## OPTIMIZATION OF ONGOING TRIPLE THERAPY AND INTENSIFICATION OF SODIUM DEPLETION

According to the 2018 ESH guidelines (3), effective treatment combines lifestyle changes (especially reducing sodium intake to less than 100 mmol/day), discontinuation of interfering substances, and the sequential addition of antihypertensive drugs to the initial triple therapy. Ultimately, replacing all current drugs by a simpler treatment regimen using single-pill combination therapy reduces pill burden and improves adherence to treatment (3).

The first step of RHTN care is to optimize the doses of current treatment or to prescribe appropriate antihypertensive drug combinations (3,5,14,15). One of the causes of RHTN is inappropriate refractory volume retention of multifactorial origin, as suggested by the low renin levels measured in patients with RHTN (25–27). BP control can thus be improved by increasing the intensity of diuretic therapy, particularly in patients with chronic kidney disease (3,5,14,15,28). The dose of the diuretic can be increased or a more potent thiazide-like diuretic (chlorthalidone and indapamide) can be used instead of hydrochlorothiazide or bendroflumethiazide if estimated GFR (eGFR)  $\geq 30$  mL/min (29–32). The use of a potassium-sparing diuretic (33) or of an aldosterone antagonist in combination (34,35) can prevent thiazide-induced hypokalaemia and improve BP control (see below).

Loop diuretics should be used when eGFR  $< 30$  mL/min (4,28,36), although small studies have shown that thiazides may retain their natriuretic and antihypertensive effects when GFR  $< 30$  mL/min (37,38). The dose or intake frequency of the loop diuretic may need to be increased in patients with severe chronic kidney disease and/or albuminuria (28,36). Regular monitoring of plasma creatinine, serum electrolyte levels and fluid status is required to

detect dehydration, hypokalaemia, hyponatraemia, hypovolaemia or renal dysfunction.

## ADDING A FOURTH ANTIHYPERTENSIVE MEDICATION: A MINERALOCORTICOID RECEPTOR BLOCKER

The fourth-line treatment should involve a mineralocorticoid receptor (MR) antagonist, such as spironolactone (Class I A recommendation) (3) or eplerenone. Eplerenone is a short-acting MR antagonist better tolerated but less potent than spironolactone (34,35). However, eplerenone has not been approved for use to treat hypertension in many European countries.

MR blockade is an effective way to decrease BP in patients with RHTN for multiple pathophysiological reasons (35,39), as shown in randomized trials and meta-analyses (40,41). The PATHWAY-2 double-blind crossover study has provided the strongest evidence in favour of the use of spironolactone as a fourth-line treatment added to a pre-existing three-drug regimen (ACEI, a CCB, and a low dose of bendroflumethiazide) in overweight patients with RHTN, eGFR  $\geq 45$  mL/min, and plasma potassium concentrations within the normal range (42). Indeed, 12-week treatment with spironolactone 25–50 mg was the most effective treatment, allowing BP control in 58% of the patients compared to 42% of those treated with doxazosin (4–8 mg), and 43% of those treated with bisoprolol (5–10 mg). However, both bisoprolol and doxazosin reduce BP more than placebo when added to background treatment. Spironolactone was more effective in those with a low renin profile on the initial triple combination therapy. This relationship was not observed for bisoprolol or doxazosin. There was a low rate of side effects, including gynecomastia, breast tenderness, menstrual irregularities in women and sexual impotence. These side effects due to antiandrogenic effect of spironolactone are known to occur in the long term (43) and may lead to treatment being stopped. Finally, the risk of hyperkalaemia may be greater in patients with chronic kidney disease, particularly if spironolactone is added to a treatment including an RAS blocker (44), making it necessary to monitor plasma potassium and creatinine concentrations closely. The efficacy and safety of spironolactone has not yet been established in patients with significant renal insufficiency.

The PATHWAY-2 study was followed by an optional 6–12 week open-label phase during which the potassium-sparing diuretic amiloride 10–20 mg once daily was given to the patients after the crossover study (45). Amiloride (10 mg once daily) reduced clinic systolic blood pressure by 20.4 mmHg (95% CI 18.3–22.5), a comparable BP decrease to that achieved with spironolactone 25 mg once daily (18.3 mmHg (16.2–20.5)) (45). Finally, the ReHOT (Resistant Hypertension Optimal Treatment) randomized study (46), comparing 12-week treatment with spironolactone (12.5–50 mg QD) or clonidine (0.1–0.3 mg BID) in Brazilian patients, showed similar rates of combined office and 24-h ambulatory BP control (20.5% vs. 20.8%), similar office BP (33.3% vs. 29.3%) and 24-h ambulatory BP monitoring (44% vs. 46.2%) control for spironolactone and clonidine, respectively (46). However, spironolactone was more efficient on some ambulatory BP endpoints. The rate of side effects reported for both spironolactone and

**General measures**

- Take into account cardiovascular or other comorbid conditions (chronic kidney disease), age, sex, ethnicity, drug-drug interactions, contraindications, previous side effects.
- Use fixed-dose combinations in a single pill, home BP monitoring, regular appointments, and the help of nurses, pharmacists and patient's family, to improve adherence to treatment.
- Regular monitoring of plasma electrolytes (K and Na) and creatinine (or cystatin C) concentrations.

**Maximize diuretic therapy in addition to a low sodium diet**

- Switch to a more potent and long-acting thiazide (chlorthalidone and indapamide) when eGFR is  $\geq 30$  mL/min/1.73 m<sup>2</sup> or to loop diuretics when eGFR is  $< 30$  mL/min/1.73 m<sup>2</sup>.
- Increase the diuretic dose.
- Monitor plasma electrolytes and creatinine concentrations.

**Add a mineralocorticoid receptor antagonist at low dose**

- Patients with eGFR  $\geq 45$  mL/min/1.73 m<sup>2</sup> and plasma K levels  $\leq 4.5$  mmol or especially in cases heart failure or left ventricular dysfunction.
- When spironolactone is contraindicated or not tolerated, bisoprolol, doxazosin, amiloride or clonidine can be used.
- Monitor plasma K and creatinine (or cystatin C) concentrations closely.

**Add other antihypertensive drugs step by step**

- A beta-blocker; monitor ECG
- An alpha-blocker
- A centrally acting alpha-agonist

**Figure 48.1** Pharmacological treatment for resistant hypertension.

clonidine was low. The patients randomized to clonidine had more frequent somnolence.

In summary, RHTN is commonly a salt-retaining state, most likely due to inappropriate aldosterone secretion (45). MR blockade by spironolactone overcomes the salt retention and resistance of hypertension to treatment. Spironolactone (25–50 mg/day) should be used in patients with RHTN but restricted to those with an eGFR  $\geq 45$  mL/min and a plasma potassium concentration  $\leq 4.5$  mmol/L (Figure 48.1), particularly in cases of a compelling indication, such as heart failure, in accordance with guidelines (3,4,28). When spironolactone is contraindicated or not tolerated, bisoprolol (42), doxazosin (42), amiloride (45) or clonidine (46) can be used for the treatment of RHTN (Figure 48.1).

The efficacy of spironolactone to reverse sodium overload and thus to lower BP in patients with RHTN may be enhanced by using a combination of loop diuretics and thiazides at low doses, or sequential nephron blockade (sequential administration of 25 mg/day spironolactone, followed by 20 and then 40 mg/day furosemide, and 5 mg/day amiloride) on top of a triple therapy including a low dose of 12.5 mg of hydrochlorothiazide, as shown in a French study (47). However, although well tolerated in this trial, sequential nephron blockade strategy requires the careful monitoring of renal function, serum electrolyte levels and fluid status, for the detection of dehydration, hypokalaemia, hyponatraemia, hypovolaemia or renal dysfunction.

### FURTHER ADDITION OF ANTIHYPERTENSIVE TREATMENTS: SEEKING SPECIALIST ADVICE

Specialist advice should be sought at a dedicated tertiary BP clinic if BP remains uncontrolled (3–5). At this stage, a stepwise addition of a beta-blocker (with exception of

atenolol), an alpha-blocker and a centrally acting alpha-agonist is preferred (Figure 48.1). Beta-blockers can be used particularly in patients with coronary artery disease, heart failure, arrhythmia or chronic kidney disease (3–5). Direct vasodilators (hydralazine or minoxidil) should be avoided, because they may induce fluid retention and tachycardia (3–5). Dual RAS blockade with ACEI and ARBs or with direct renin inhibitors should not be used (3,4) because such combinations (i) are not effective for lowering BP 47, and (ii) are associated with a higher risk of hyperkalaemia, hypotension and acute renal failure (48).

The complexity of the multidrug therapeutic regimens used in patients with RHTN increases the likelihood of drug-related side effects and may contribute to the lack of adherence to treatment of patients who may be taking large numbers of other drugs for comorbid conditions.

## IMPROVING THE EFFICACY OF ANTIHYPERTENSIVE TREATMENTS

### DETECTING NONADHERENCE AND IMPROVING ADHERENCE TO ANTIHYPERTENSIVE TREATMENT

Nonadherence to antihypertensive medications and lifestyle measures is a key contributing factor to RHTN (49,50). Nonadherence is associated with poor cardiovascular prognosis (51,52). Several disease-, physician-, treatment- and patient-related factors, either alone or in combination, promote nonadherence to treatment and are common to all chronic diseases, including hypertension (49,50).

Various direct and indirect methods for assessing adherence to drug treatments have been developed (49,50). Some methods are easy to use (standardized questionnaire, determination of physiological variables), whereas others, such as drug detection or the direct observation of treatment intake, are much more difficult to implement (49,50). About 50% of patients attending specialized BP clinics for RHTN have been found not to be complying with the prescribed drug regimen (53–57).

Multiple approaches are required to improve compliance, adherence and long-term persistence, but their long-term efficacy remains to be established (58,59). Approaches include improving the physician-patient relationship, patient education, the use of reminders, use of electronic pill monitors (60), frequent clinic visits, self-monitoring of BP, patient empowerment and self-management (61), text messaging and assistance from other healthcare providers, including pharmacists and nurses and families (58,62,63). However, the complexity of these interventions may make them difficult to implement in everyday practice. Technology-based interventions for education, counseling, self-monitoring, feedback and electronic reminders are increasingly being used, but their efficacy for improving treatment adherence is inconsistent (64). The preferential use of once-daily single-pill triple combination therapies reduces pill burden (63), simplifies treatment regimens without increasing the incidence of side effects and improves compliance with treatment (64,65).

## REDUCING CLINICAL INERTIA

Clinical inertia is another major factor contributing to inadequate BP control and other associated risk factors. An analysis of electronic record data at 200 US clinical sites showed that only 4.7% of the patients with apparent RHTN were prescribed optimal triple therapy including a diuretic and at least two other BP drugs at a dose at least 50% the maximum dose recommended for hypertension (65). There are many reasons for clinical inertia and potential barriers to compliance with guidelines for physicians (66). The use of strict protocol-based treatment algorithms may overcome clinical inertia by providing healthcare providers with simple, accessible prescription rules (67). Such algorithms can be incorporated into clinical support decision tools, but the resulting improvement in BP control in patients with RHTN is uncertain because of nonadherence of patients to treatment (57).

## DISCONTINUATION OF INTERFERING SUBSTANCES

Several drugs prescribed for conditions other than hypertension can increase BP or blunt the BP-lowering effect of antihypertensive treatments (see for review (68)). Finally, some drugs may directly or indirectly interfere with the pharmacokinetic and/or pharmacodynamic profile of the antihypertensive drugs (69). Careful evaluation of the drugs taken by patients for conditions other than cardiovascular diseases, through the completion of a standardized questionnaire (70) or the use of drug–drug interaction-checking websites, can help to identify drug-related hypertension.

## SUMMARY

RHTN is defined as the failure to lower BP values to the target value despite appropriate treatment with optimal doses of at least three antihypertensive drugs including an RAS blocker, a long-acting CCB and a thiazide (or thiazide-like) diuretic. Pseudoresistance should be excluded by 24-h ambulatory or home BP monitoring and non-adherence to medications by drug monitoring. RHTN management combines lifestyle changes, the discontinuation of interfering substances, and the sequential addition of antihypertensive drugs to the initial triple therapy (diuretic, RAS blocker and CCB), including spironolactone as a fourth-line treatment, followed by sequential sympathetic nervous system blockade. New pharmacological treatments targeting new pathways and device-based approaches aiming to decrease sympathetic tone, including renal denervation and baroreceptor stimulation, are currently being developed. However, it will take a long time to evaluate the efficacy and safety of these new approaches thoroughly. In the meantime, the use of appropriate and personalized daily doses of the available drug – especially triple combinations of a diuretic, RAS blocker and CCB in a single pill, and efforts to decrease physician inertia, to improve compliance with treatment and access to healthcare and to decrease treatment costs remain major objectives for reducing the incidence of RHTN to decrease target-organ damage and improve cardio- and cerebrovascular prognosis.

## REFERENCES

1. Kearney PM, Whelton M, Reynolds K et al. Global burden of hypertension: Analysis of worldwide data. *Lancet* 2005; 365: 217–223.
2. Chobanian AV. Shattuck lecture. The hypertension paradox – more uncontrolled disease despite improved therapy. *N Engl J Med* 2009; 361: 878–887.
3. Williams B, Mancia G, Spiering W et al. ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens* 2018; 36(10): 1953–2041.
4. Krause T, Lovibond K, Caulfield M et al. Management of hypertension: Summary of nice guidance. *BMJ* 2011; 343: d4891.
5. Calhoun DA, Jones D, Textor S et al. Resistant hypertension: Diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association professional education committee of the council for high blood pressure research. *Hypertension* 2008; 51: 1403–1419.
6. Cuspidi C, Macca G, Sampieri L et al. High prevalence of cardiac and extracardiac target organ damage in refractory hypertension. *J Hypertens* 2001; 19: 2063–2070.
7. Muiesan ML, Salvetti M, Rizzoni D et al. Resistant hypertension and target organ damage. *Hypertens Res* 2013; 36: 485–491.
8. Daugherty SL, Powers JD, Magid DJ et al. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation* 2012; 125: 1635–1642.
9. Judd E, Calhoun DA. Apparent and true resistant hypertension: Definition, prevalence and outcomes. *J Hum Hypertens* 2014; 28: 463–468.
10. Achelrod D, Wenzel U, Frey S. Systematic review and meta-analysis of the prevalence of resistant hypertension in treated hypertensive populations. *Am J Hypertens* 2015; 28: 355–361.
11. Sinnott SJ, Smeeth L, Williamson E, Douglas IJ. Trends for prevalence and incidence of resistant hypertension: Population based cohort study in the UK 1995–2015. *BMJ* 2017; 358: j3984.
12. Tanner RM, Calhoun DA, Bell EK et al. Prevalence of apparent treatment-resistant hypertension among individuals with CKD. *Clin J Am Soc Nephrol* 2013; 8: 1583–j1590.
13. de la Sierra A, Segura J, Banegas JR et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of



- ambulatory blood pressure monitoring. *Hypertension* 2011; 57: 898–902.
14. Myat A, Redwood SR, Qureshi AC et al. Resistant hypertension. *BMJ* 2012; 345: e7473.
  15. Vongpatanasin W. Resistant hypertension: A review of diagnosis and management. *JAMA* 2014; 311: 2216–e2224.
  16. Pimenta E, Gaddam KK, Oparil S et al. Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: Results from a randomized trial. *Hypertension* 2009; 54: 475–481.
  17. Shimbo D, Levitan EB, Booth JN, 3rd et al. The contributions of unhealthy lifestyle factors to apparent resistant hypertension: Findings from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *J Hypertens* 2013; 31: 370–376.
  18. Martins LC, Figueiredo VN, Quinaglia T et al. Characteristics of resistant hypertension: Ageing, body mass index, hyperaldosteronism, cardiac hypertrophy and vascular stiffness. *J Hum Hypertens* 2011; 25: 532–538.
  19. Ruttanaumpawan P, Nopmaneejumrulers C, Logan AG et al. Association between refractory hypertension and obstructive sleep apnea. *J Hypertens* 2009; 27: 1439–1445.
  20. Hu X, Fan J, Chen S et al. The role of continuous positive airway pressure in blood pressure control for patients with obstructive sleep apnea and hypertension: A meta-analysis of randomized controlled trials. *J Clin Hypertens (Greenwich)* 2015; 17: 215–222.
  21. Martinez-Garcia MA, Capote F, Campos-Rodriguez F et al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: The HIPARCO randomized clinical trial. *JAMA* 2013; 310: 2407–2415.
  22. Muxfeldt ES, Margallo V, Costa LM et al. Effects of continuous positive airway pressure treatment on clinic and ambulatory blood pressures in patients with obstructive sleep apnea and resistant hypertension: A randomized controlled trial. *Hypertension* 2015; 65: 736–742.
  23. Campos-Rodriguez F, Martinez-Alonso M, Sanchez-de-la-Torre M, Barbe F. Long-term adherence to continuous positive airway pressure therapy in non-sleepy sleep apnea patients. *Sleep Med* 2016; 17: 1–6.
  24. Bratton DJ, Gaisl T, Wons AM, Kohler M. CPAP vs mandibular advancement devices and blood pressure in patients with obstructive sleep apnea: A systematic review and meta-analysis. *JAMA* 2015; 314: 2280–2293.
  25. Eide IK, Torjesen PA, Drolsum A et al. Low-renin status in therapy-resistant hypertension: A clue to efficient treatment. *J Hypertens* 2004; 22: 2217–2226.
  26. Gaddam KK, Nishizaka MK, Pratt-Ubunama MN et al. Characterization of resistant hypertension: Association between resistant hypertension, aldosterone, and persistent intravascular volume expansion. *Arch Intern Med* 2008; 168: 1159–1164.
  27. Calhoun DA. Hyperaldosteronism as a common cause of resistant hypertension. *Annu Rev Med* 2013; 64: 233–247.
  28. Kidney disease improving global outcomes (KDIGO) blood pressure work group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl* 2012; 2: 337–414.
  29. Roush GC, Ernst ME, Kostis JB et al. Head-to-head comparisons of hydrochlorothiazide with indapamide and chlorthalidone: Antihypertensive and metabolic effects. *Hypertension* 2015; 65: 1041–1046.
  30. Ernst ME, Carter BL, Goerdt CJ et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension* 2006; 47: 352–358.
  31. Pareek AK, Messerli FH, Chandurkar NB et al. Efficacy of low-dose chlorthalidone and hydrochlorothiazide as assessed by 24-h ambulatory blood pressure monitoring. *J Am Coll Cardiol* 2016; 67: 379–389.
  32. Peterzan MA, Hardy R, Chaturvedi N, Hughes AD. Meta-analysis of dose-response relationships for hydrochlorothiazide, chlorthalidone, and bendroflumethiazide on blood pressure, serum potassium, and urate. *Hypertension* 2012; 59: 1104–1109.
  33. Roush GC, Ernst ME, Kostis JB et al. Dose doubling, relative potency, and dose equivalence of potassium-sparing diuretics affecting blood pressure and serum potassium: Systematic review and meta-analyses. *J Hypertens* 2016; 34: 11–19.
  34. Jansen PM, Danser AH, Imholz BP, van den Meiracker AH. Aldosterone-receptor antagonism in hypertension. *J Hypertens* 2009; 27: 680–691.
  35. Colussi G, Catena C, Sechi LA. Spironolactone, eplerenone and the new aldosterone blockers in endocrine and primary hypertension. *J Hypertens* 2013; 31: 3–15.
  36. Tamargo J, Segura J, Ruilope LM. Diuretics in the treatment of hypertension. Part 2: Loop diuretics and potassium-sparing agents. *Expert Opin Pharmacother* 2014; 15: 605–621.
  37. Dussol B, Moussi-Frances J, Morange S et al. A pilot study comparing furosemide and hydrochlorothiazide in patients with hypertension and stage 4 or 5 chronic kidney disease. *J Clin Hypertens (Greenwich)* 2012; 14: 32–37.
  38. Agarwal R, Sinha AD, Pappas MK, Ammous F. Chlorthalidone for poorly controlled hypertension in chronic kidney disease: An interventional pilot study. *Am J Nephrol* 2014; 39: 171–182.
  39. Epstein M, Duprez DA. Resistant hypertension and the pivotal role for mineralocorticoid receptor antagonists: A clinical update - 2016. *Am J Med* 2016; 129(7): 661–666.
  40. Dahal K, Kunwar S, Rijal J et al. The effects of aldosterone antagonists in patients with resistant hypertension: A meta-analysis of randomized and nonrandomized studies. *Am J Hypertens* 2015; 28: 1376–1385.
  41. Sinnott SJ, Tomlinson LA, Root AA et al. Comparative effectiveness of fourth-line anti-hypertensive agents in resistant hypertension: A systematic review and meta-analysis. *Eur J Prev Cardiol* 2017; 24: 228–238.
  42. Williams B, MacDonald TM, Morant S et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): A randomised, double-blind, crossover trial. *Lancet* 2015; 386: 2059–2068.
  43. Jeunemaitre X, Charru A, Chatellier G et al. Long-term metabolic effects of spironolactone and thiazides combined with potassium-sparing agents for treatment of essential hypertension. *Am J Cardiol* 1988; 62: 1072–1077.
  44. Bolognani D, Palmer SC, Navaneethan SD, Strippoli GF. Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev* 2014; 4: CD007004.
  45. Williams B, MacDonald TM, Morant SV et al. British Hypertension Society Programme of Prevention and Treatment Of Hypertension With Algorithm Based Therapy (PATHWAY) Study Group. Endocrine and haemodynamic changes in resistant hypertension, and blood pressure responses to spironolactone or amiloride: The pathway-2 mechanisms substudies. *Lancet Diabetes Endocrinol* 2018; 6(6): 464–475.
  46. Krieger EM, Drager LF, Giorgi DMA et al. REHOT Investigators. Spironolactone versus clonidine as a fourth-drug therapy for resistant hypertension: The REHOT Randomized Study (Resistant Hypertension Optimal Treatment). *Hypertension* 2018; 71: 681–690.
  47. Bobrie G, Frank M, Azizi M et al. Sequential nephron blockade versus sequential renin-angiotensin system blockade in resistant hypertension: A prospective, randomized, open blinded endpoint study. *J Hypertens* 2012; 30: 1656–1664.
  48. Makani H, Bangalore S, Desouza KA et al. Efficacy and safety of dual blockade of the renin-angiotensin system: Meta-analysis of randomised trials. *BMJ* 2013; 346: f360.
  49. Burnier M, Wuerzner G, Struijker-Boudier H, Urquhart J. Measuring, analyzing, and managing drug adherence in resistant hypertension. *Hypertension* 2013; 62: 218–f225.
  50. Berra E, Azizi M, Capron A et al. Evaluation of adherence should become an integral part of assessment of patients with apparently treatment-resistant hypertension. *Hypertension* 2016; 68(2): 297–306.
  51. Simpson SH, Eurich DT, Majumdar SR et al. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ* 2006; 333: 15.
  52. Mazzaglia G, Ambrosioni E, Alacqua M et al. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. *Circulation* 2009; 120: 1598–1605.
  53. Jung O, Gechter JL, Wunder C et al. Resistant hypertension? Assessment of adherence by toxicological urine analysis. *J Hypertens* 2013; 31: 766–774.
  54. Strauch B, Petrak O, Zelinka T et al. Precise assessment of noncompliance with the antihypertensive therapy in patients with resistant hypertension using toxicological serum analysis. *J Hypertens* 2013; 31: 2455–2461.
  55. Patel P, Gupta PK, White CM et al. Screening for non-adherence to antihypertensive treatment as a part of the diagnostic pathway to renal denervation. *J Hum Hypertens* 2016 Jun; 30(6): 368–373.
  56. Tomaszewski M, White C, Patel P et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. *Heart* 2014; 100: 855–861.
  57. Azizi M, Pereira H, Hamdidouche I et al. Adherence to antihypertensive treatment and the blood pressure-lowering effects

- of renal denervation in the renal denervation for hypertension (DENERHTN) trial. *Circulation* 2016; 134: 847–857.
58. Nieuwlaat R, Wilczynski N, Navarro T et al. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2014; 11: CD000011.
  59. Hamdidouche I, Jullien V, Boutouyrie P et al. Drug adherence in hypertension: From methodological issues to cardiovascular outcomes. *J Hypertens* 2017; 35: 1133–1144.
  60. Christensen A, Osterberg LG, Hansen EH. Electronic monitoring of patient adherence to oral antihypertensive medical treatment: A systematic review. *J Hypertens* 2009; 27: 1540–1551.
  61. McManus RJ, Mant J, Haque MS et al. Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: The TASMIN-SR randomized clinical trial. *JAMA* 2014; 312: 799–808.
  62. Haynes RB, McDonald HP, Garg AX. Helping patients follow prescribed treatment: Clinical applications. *JAMA* 2002; 288: 2880–2883.
  63. Schroeder K, Fahey T, Ebrahim S. How can we improve adherence to blood pressure-lowering medication in ambulatory care? Systematic review of randomized controlled trials. *Arch Intern Med* 2004; 164: 722–732.
  64. Mistry N, Keepanasseril A, Wilczynski NL et al. Technology-mediated interventions for enhancing medication adherence. *J Am Med Inform Assoc* 2015; 22: e177–e193.
  65. Egan BM, Zhao Y, Li J et al. Prevalence of optimal treatment regimens in patients with apparent treatment-resistant hypertension based on office blood pressure in a community-based practice network. *Hypertension* 2013; 62: 691–697.
  66. Casey DE J. Why don't physicians (and patients) consistently follow clinical practice guidelines? *JAMA Intern Med* 2013; 173: 1581–1583.
  67. Feldman RD, Zou GY, Vandervoort MK et al. A simplified approach to the treatment of uncomplicated hypertension: A cluster randomized, controlled trial. *Hypertension* 2009; 53: 646–653.
  68. Rossi GP, Seccia TM, Maniero C, Pessina AC. Drug-related hypertension and resistance to antihypertensive treatment: A call for action. *J Hypertens* 2011; 29: 2295–2309.
  69. Grossman E, Messerli FH. Drug-induced hypertension: An unappreciated cause of secondary hypertension. *Am J Med* 2012; 125: 14–22.
  70. Postel-Vinay N, Bobrie G, Steichen O et al. HY-quest, standardized patient questionnaire to be completed at home before a first visit for hypertension: A validation study in specialized centres in France. *J Hypertens* 2014; 32: 693–698.



# INTERVENTIONAL THERAPIES FOR ESSENTIAL HYPERTENSION

# 49

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and Vassilios Papademetriou*

## INTRODUCTION

Despite modern pharmacological therapies, a significant proportion of hypertensive patients remains uncontrolled, with only 35–40% remaining within target blood pressure (BP). In order to address the unmet need of optimal BP control technological advancements, the use of device-based therapies has been introduced to reduce BP in the setting of essential hypertension. These interventional therapies mainly modulate diverse components of the sympathetic nervous system (SNS) and its interplay with the vasculature. In this chapter an update on these promising therapies is provided with special focus on renal denervation (RDN), which is currently the most-studied interventional approach for BP reduction in essential hypertension.

## BARORECEPTOR ACTIVATION THERAPY

### BACKGROUND AND RATIONALE

It has been over 50 years since experimental and clinical studies provided the first evidence that by applying electrical energy to the carotid sinus nerve it is possible to lower BP (1). Parallel to RDN history, insufficient technology and surgical side effects did not allow for the treatment to evolve further.

Arterial baroreceptors are situated at the carotid sinus and the aortic arch and regulate BP within a narrow range. When BP increases, these receptors are activated and trigger a reflex, sending afferent nerve signals to the nucleus tractus solitarius in the central nervous system; the subsequent decrease in sympathetic efferent output leads to BP reduction, and the increase in parasympathetic activity results in a decrease in heart rate. In the setting of chronic hypertension, carotid baroreceptor function is reset, and they operate at a greater mean BP (2).

The concept of baroreceptor activation therapy (BAT) is based on electrical stimulation of the region where the carotid baroreceptors are located, in order to mimic endogenous signalling. Afferent nerve traffic from the baroreceptors to

cardiovascular control centres of the brain is thus enhanced, and sympathetic outflow and BP are reduced. This modality was initially tried in canine models, in which it was shown that a 1-week BAT produces rapid BP reduction that is sustained through the entire stimulation period (3).

### RHEOS CAROTID PACEMAKER SYSTEM

The first-generation Rheos carotid pacemaker system is comprised of an implantable pulse generator and two sets of bipolar, perivascular carotid sinus leads as well as a radiofrequency couple programmer (Figure 49.1). Under general anaesthesia, the generator is surgically implanted in a pre-pectoral pocket and the leads are tunnelled subcutaneously and applied bilaterally to the carotid sinuses through a surgical incision that resembles carotid endarterectomy; their positioning is based on the greatest decrease in BP and heart rate with current delivery applied at 1-V increments up to 7.0 V (4). The electrical energy required to stimulate the baroreceptor area is expressed as power and is calculated from pulse width and amplitude, and frequency for a given impedance. Battery life of the Rheos generator is approximately 1.5–2 years.

The Rheos system has been studied in three multicentre trials. The initial evaluation was performed in a phase II safety and feasibility study in 10 patients with resistant hypertension under a median of six drugs (4). The post-implantation dose-response test revealed a systolic BP decrease at a range of 22–104 mmHg. Accordingly, the non-randomised DEBuT-HT trial was performed in 45 severe resistant hypertension patients (mean BP 179/105 mmHg under a median of five drugs) (5). A sustained decrease in clinic BP by 21/12 mmHg at 3 months and 33/22 mmHg at 2 years (in 37 and 17 patients, respectively) under a stable number of drugs was shown. A total of seven serious adverse events was noted, including infections needing device explantation, movement of the generator and perioperative stroke.

These encouraging results were followed by the double-blind, randomised, parallel-design, placebo-controlled phase III Rheos Pivotal Trial on 265 patients with severe

resistant hypertension (6). The device was implanted in all participants, and BAT was engaged in a 2:1 fashion either for the first 6 months (active group) or in a delayed manner after the 6-month visit (control group). At 6 months, decreases in clinic systolic BP by 16 mmHg in the active group and 9 mmHg in the control group ( $p = 0.08$ ) were recorded, with sustained efficacy at 12 months (7). The trial failed the acute 6-month responder efficacy endpoint ( $>10$  mmHg systolic BP drop) but not the ancillary endpoint of subjects attaining a systolic BP below 140 mmHg (42% in the treatment group vs. 24% in the control group). Of interest, a post hoc analysis revealed that right-sided unilateral BAT had a greater effect on BP compared to bilateral or left-sided BAT (8). The study, however, raised safety concerns related to surgical complications and facial nerve injury.

Data from the 6-year open follow-up of 383 patients included in any of the three trials provide long-term efficacy and safety data of the device (9). Office BP fell from  $179 \pm 24/103 \pm 16$  mmHg to  $144 \pm 28/85 \pm 18$  mmHg ( $p < 0.0001$ ), and the greatest BP drop was documented at 6 months and sustained thereafter. The treatment effect was more evident in patients with heart failure signs and smaller in those with isolated systolic hypertension. About a quarter of patients were able to reduce their median drug number by half. The procedure proved overall safe. Out of a total of 335 serious adverse events recorded, 26 were related to the procedure or the system and included generator migration, lead malfunction or migration and episodes of hypotension.

## BAROSTIM NEO

The Barostim neo (CVRx) is a second-generation, improved version of the Rheos device and features a smaller pulse generator with a longer-lasting battery and a simpler, single-button, 2-mm lead that is unilaterally placed at the right carotid sinus (Figure 49.1). The surgical procedure, performed under conscious sedation, has an improved safety profile due to the need for only a small incision for electrode placement and no exposure of the external carotid artery.

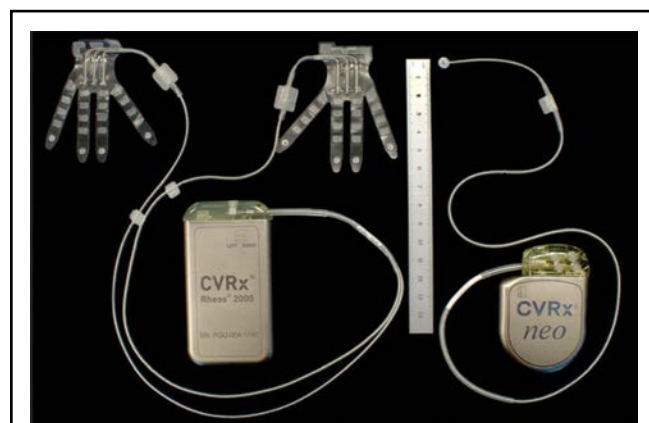


**Figure 49.1** The original CVRxRheos device and the second-generation Barostim neo. (Courtesy of CVRx.)

The preliminary Barostim neo trial was a single-arm open-label study on 30 patients with RHTN in whom device programming was individually tailored (10). Resultant decreases in BP were similar to bilateral therapy. At 6 months, a significant decrease in clinic BP by  $26 \pm 4/12 \pm 2.5$  mmHg was documented. Significant decreases were also observed in patients with prior RDN, similar to the other BAT studies. The study documented a pacemaker-like safety profile, with all of three complications associated with the generator pocket. However, a limitation of most BAT studies is the utilization of office BP for the efficacy endpoint. A recent uncontrolled study on 51 patients with resistant hypertension who underwent treatment with the Barostim neo showed that 24-h BP was significantly reduced by  $8 \pm 6/5 \pm 2$  mmHg at 6 months (11). The Barostim neo Hypertension Pivotal Trial is a randomised controlled trial on resistant hypertension patients that will shed more light on the safety and efficacy of the system ([clinicaltrials.gov/NCT01679132](https://clinicaltrials.gov/NCT01679132)).

## MOBIUSHD

The MobiusHD (Vascular Dynamics, Inc.) is an endovascular, nitinol, self-expanding cuboid stent that is unilaterally applied to the carotid sinus through the less invasive endovascular femoral approach (Figure 49.2). The device increases carotid sinus wall strain by inducing geometric changes at the level of the carotid bulb, without affecting pulsatile or laminar flow. As the increased wall strain is sensed as increased pressure, the device amplifies baroreceptor sensitivity and feedback in order to lower sympathetic activity and BP.

Recently, the results of the Controlling and Lowering Blood Pressure with the MobiusHD-First in Man (CALM-FIM\_EUR) study were reported (12). The study was a multicentre, open-label, safety and proof-of-principle trial in patients with severe resistant hypertension (mean office BP  $184/109$  mmHg on a mean of 4.4 drugs). Exclusion criteria



**Figure 49.2** The cuboid, stent-like MobiusHD device designed to reshape the carotid sinus. (Courtesy of Vascular Dynamics.)

included possible baroreflex failure or autonomic neuropathy. Lowering of BP was already evident in the first 24 hours after implantation. Significant reductions in office and 24-h BP were documented (24/12 mmHg and 17/14 mmHg respectively) at 6 months. The few serious adverse events included episodes of hypotension and wound infection. Blinded, sham-controlled trials (clinicaltrials.gov/NCT02804087) shall investigate the device safety and efficacy further.

## CENTRAL ILIAC ARTERIOVENOUS ANASTOMOSIS

### BACKGROUND PHYSIOLOGY AND RATIONALE

While other interventional therapies of hypertension primarily target the SNS, the central iliac arteriovenous (AV) anastomosis seeks to add a low-resistance, high-compliance venous segment to the arterial tree in order to reduce systemic vascular resistance and restore the Windkessel model of elastic aortic function (Figure 49.3). The concept of the creation of a fixed-calibre central AV fistula was initially developed for patients with chronic obstructive pulmonary disease. The desired effect was to increase central venous oxygenation as well as oxygen saturation in pulmonary shunts not participating in exchange of gases (13). Moderate results regarding exercise capacity along with adverse events restricted the interest in further development of the procedure for this indication (14).

The creation of an AV fistula results in blood flow parallel to the systemic circulation, leading to a reduction in systemic vascular resistance and cardiac afterload (15). It is well known that peripheral AV fistulae in haemodialysis patients are accompanied by decreases in BP and peripheral resistance (16,17). However, BP reduction due to the shunt in turn leads to sympathetic activation. The increase in venous return and sympathetic activation result in an increase in cardiac output. The percentage of the cardiac output that the shunt holds needs therefore to reach a threshold over which any increase in systemic resistance and cardiac output fail

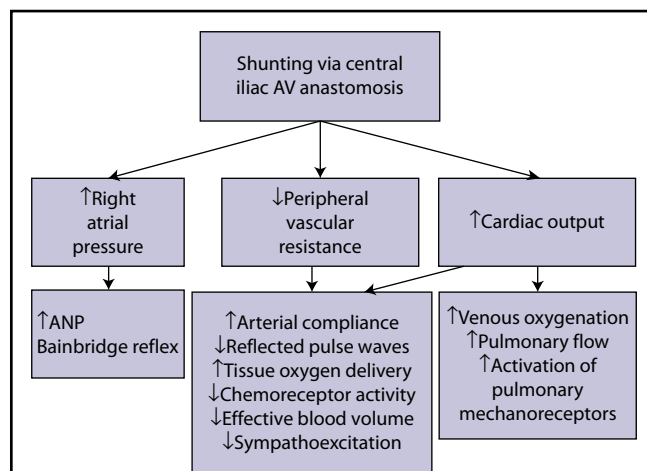


**Figure 49.3** Physiological changes after creation of a central iliac anastomosis. (Adapted by Burchell AE et al. *Hypertension* 2014; 64(1): 6–12.)

to maintain the baseline BP, eventually leading to its reduction. On the other hand, the increased cardiac preload leads to higher right atrial and pulmonary capillary wedge pressure that may attenuate the baroreceptor reflex (along with sympathetic activation) as well as trigger the release of natriuretic peptides. Furthermore, a central AV anastomosis reduces effective arterial blood volume to a new baseline without depleting other volume capacitance spaces, and thus without neurohormonal activation. This is of particular interest for the ageing aorta, where the stress-strain curve shifts to the left; after the anastomosis, for any increase in intravascular volume, a milder increase in BP is expected, restoring arterial compliance (18).

### THE ARTERIOVENOUS COUPLER

The ROX AV coupler (ROX Medical) is a nitinol-based, self-expanding device resembling a coronary stent with shape memory, allowing it to adopt a preformed figure after deployment (Figure 49.4). The implantation procedure is performed in the catheterization laboratory or the endovascular operating room. In the beginning, a 4F arterial and 11F venous sheath are placed in either the right or left common femoral artery and ipsilateral vein, with a 2-cm height difference. A crosshair spiral guidewire is advanced

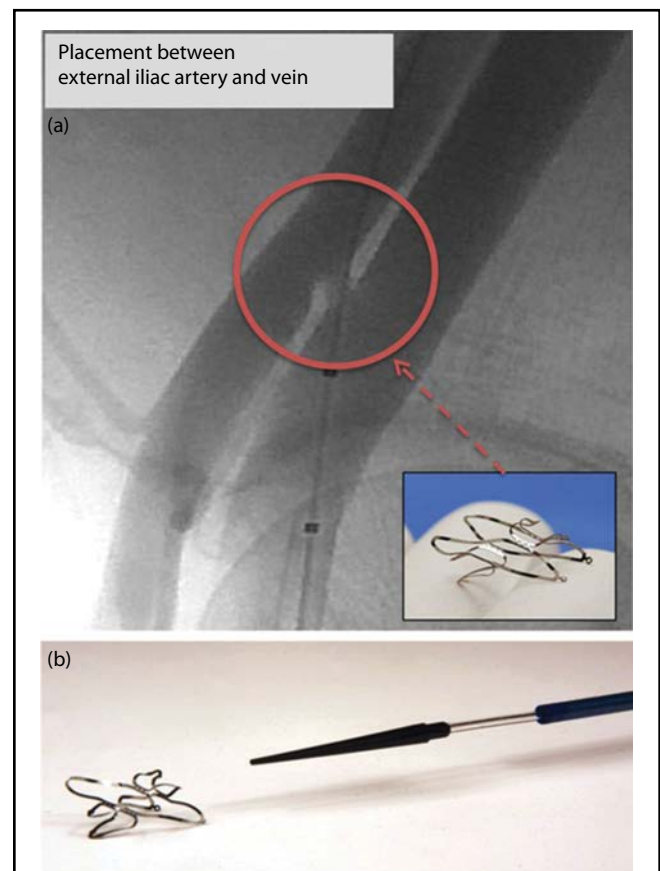


**Figure 49.4** The arteriovenous ROX coupler is a self-expanding, stent-like device that is placed under fluoroscopic guidance. (a) The created anastomosis as shown in angiography; (b) the arteriovenous ROX coupler device. (Courtesy of ROX Medical.)

through the arterial sheath to mark the desired anastomosis location, 2–4 cm above the femoral head. At that point, the external iliac artery should be free of calcium and have a diameter of at least 5 mm, while the space between artery and vein should be less than 3 mm. A micropuncture crossing needle is then introduced through the venous sheath in order to pierce through the venous and arterial walls. A crossing wire is advanced through the crossing needle, and the latter is removed. The ROX coupler delivery system, featuring a flexible tip, is then advanced over the crossing wire, and the arterial arms of the coupler are deployed first. The final anastomotic passage of a 4 mm diameter is achieved with the inflation of a balloon catheter within the coupler. Fluoroscopic guidance is used to optimize the procedure and ensure correct positioning and sizing of the anastomosis. Eventually, the device allows for controlled shunting of 800–1000 mL/min. A significant asset of the AV coupler is the direct assessment of procedural success through visualization with contrast, palpation of a thrill, auscultation of a bruit and most importantly, by the instant drop in systolic BP, which is reversible with balloon reocclusion. The anastomosis itself is reversible with the use of a covered stent.

Following trials of patients with pulmonary disease showing significant reductions in BP (19), principal study data involve patients with significantly uncontrolled hypertension. Contraindications have included previous thromboembolism and pulmonary hypertension or high pulmonary capillary wedge pressure, secondary hypertension and renal denervation within the previous 6 months.

The ROX CONTROL HTN study was a multicentre safety and efficacy, open-label trial on 83 patients with uncontrolled systolic BP (office BP at 175/100 mmHg) randomised 1:1 to coupler implantation plus current drug treatment or drug treatment alone (20). Significant reductions in the coupler group, unlike the control group, were observed in the intention to treat analysis at 6 months in both office and 24-h systolic BP (by  $27 \pm 24$  mmHg and  $14 \pm 19$  mmHg respectively,  $p < 0.0001$  for both). Highly significant BP reductions were also observed in patients who had previously undergone RNA. In a post hoc analysis of the trial data, it was also shown that the anastomosis reduces BP to a similar extent in patients with either combined or isolated systolic hypertension (21). A total of 25 procedure- or device-related events were recorded that resolved without sequelae. There were no cases of coupler migration or spontaneous closure reported. However, 29% of participants developed lower-extremity oedema in the following months due to iliac vein stenosis and were treated with venoplasty.

More recently, the available 1-year results of the active treatment group of the ROX CONTROL HTN study were published (22). A sustained reduction in office and ambulatory systolic BP (by  $25.1 \pm 23.3$  mmHg and  $12.6 \pm 17.4/15.3 \pm 9.7$  mmHg respectively,  $p < 0.0001$  for both) was noted. Rates of venous stenosis were again high (33% of patients) and all cases were treated with venous stenting. Overall, the stenosis develops upstream from the conduit as a result of venous intima hyperplasia due to turbulent flow. It is more often on the left side and is associated with ipsilateral limb swelling and an increase in BP.

The promising results have given the green light for the CONTROL HTN-2, a randomised, sham-controlled (arterial puncture) study of up to 500 uncontrolled hypertensive patients (office systolic BP  $>155$  mmHg) that is expected to be completed in 2019 (clinicaltrials.gov/

NCT02895386). The primary endpoint of the study shall be the mean ambulatory systolic BP change at 6 months. This trial, along with a running global registry (clinicaltrials.gov/NCT01885390), are expected to clarify the efficacy and accompanying cardiac adaptations of the device, as well as provide better understanding of the potential adverse events, that apart from venous stenosis include high output sequelae and venous stenosis.

## OTHER INTERVENTIONAL TREATMENTS

A number of impressive interventional modalities for the treatment of HTN are currently under investigation. Research data are very limited and mostly at a phase I or II trial level, and carefully designed studies are needed to identify their clinical use.

## CAROTID BODY ABLATION

The carotid bodies are peripheral chemoreceptors at the bifurcations of the common carotid arteries that are very sensitive to small changes in blood flow, oxygen, carbon dioxide and pH. Inappropriate activation of the carotid bodies, accompanied by sympathetic overactivity, has been observed in hypertension and sleep apnoea. Bilateral resection was performed in the past for the treatment of asthma but was abandoned due to decreased efficacy (23). Unilateral surgical carotid body resection has been recently proposed for BP lowering, acting through a reduction in afferent sympathetic activity from the carotid body (24). The procedure is performed under general or local anaesthesia with sedation, and it involves isolation of tissue within the intercarotid septum, ligation at the saddle of the bifurcation and excision of the septal tissue.

In a proof-of-concept study in 15 patients with resistant hypertension (mean office systolic BP:  $168 \pm 7$  mmHg on 5.7 drugs), the procedure was shown to be of acceptable safety, and ventilatory response to hypoxia was maintained (25). Overall, no significant change was observed in BP, but a significant decrease was noted in the eight responders with high carotid tone (by 23/12 mmHg) along with a decrease in muscle sympathetic activity. An endovascular as well as a chemical block approach to carotid body modulation are under investigation (clinicaltrials.gov/NCT02099851 and NCT02519868, respectively).

## DEEP BRAIN STIMULATION

The periaqueductal and periventricular grey matter has been shown to be associated with heart rate and BP in animals. The potential use of deep brain stimulation for BP lowering was first identified in patients with neuropathic pain (26). A number of case reports have shown that continuous deep brain stimulation with multipolar electrodes, surgically implanted with a magnetic resonance-guided stereotactic approach, may lead to significant and sustained drops in BP (27,28). An accompanying reduction in muscle sympathetic nerve activity has been noted. The proposed mechanisms include a resetting of neural networks that manage sympathetic outflow and a decrease in systemic vascular resistance.



## MEDIAN NERVE STIMULATION

Stimulation of the median nerve may improve BP through the modulation of the SNS. The electroceutical coin (eCoin by Valencia Technologies) offers reversible, low frequency stimulation to the median nerve. The procedure involves two coin-sized stimulators that are implanted subcutaneously and induce sympathoinhibition. In an unpublished, multicentre, sham-controlled trial in 48 patients with resistant hypertension, implantation of the eCoin in both arms was associated with a significant decrease in office BP by  $10 \pm 21$  mmHg (29).

## VAGAL NERVE STIMULATION

The vagus nerve is the main provider of parasympathetic innervation of the heart. Preclinical data has shown that vagal nerve stimulation may reduce BP without producing bradycardia or bradypnea (30). An implantable vagal nerve neuro stimulator system has been tested in patients with heart failure, with improvements in left ventricular dimensions and functional capacity (31). Electrical stimulation is reversible by switching off the device. In a randomised placebo-controlled trial, transcutaneous vagus nerve stimulation via the auricular branch performed in 30 healthy individuals was associated with improvements in baroreflex sensitivity (32).

## RENAL DENERVATION THERAPY

### BACKGROUND PHYSIOLOGY AND RATIONALE

In the pathogenesis and evolution of the hypertensive disease and its sequelae SNS in tandem with renin–angiotensin–aldosterone axis constitute major contributors that are inter-related (33,34). This sympathetic influence on the heart, vasculature, kidney function and diverse humoral factors is one of the key mechanisms for BP regulation and progression of hypertension-mediated organ damage (33,34).

The two most established methods for quantification of sympathetic overdrive are the estimation of the muscle sympathetic nerve activity and the norepinephrine spillover technique (35). By these means it was shown that younger hypertensive patients exhibit more pronounced activation of sympathetic tone compared to older patients, while all hypertensive phenotypes are characterized by autonomic system imbalance. Based on the above modulation of SNS activity for the management of malignant hypertension, surgical sympathectomy was introduced (36) but later abandoned due to significant side effects and the development of antihypertensive drugs (36).

In patients with resistant hypertension, RDN by disrupting renal nerves through application of transluminal energy causes a decrease in the efferent and afferent SNS activity (37–39). The efferent nerves augment renal vascular resistance, blunt the renal blood flow and increase sodium and water reabsorption by the kidneys, and on the other hand the afferent fibres transmit signals of kidney injury and ischemia to the central nervous system, contributing to the vicious cycle of SNS overdrive and hypertension. Animal and human data support the decrease in

SNS tone after RDN (37–39). This was shown by reduction of norepinephrine content in the kidneys, decrease in nor-adrenaline spillover and muscle sympathetic nerve activity after RDN. Notably, the alterations of sympathetic drive were not related to the extent of BP change, underlying the complex pathophysiology of hypertension (38–40).

### FIRST PROOF-OF-CONCEPT STUDIES

The first observational and randomised studies using radiofrequency energy to achieve RDN in patients with resistant HT have shown positive results in terms of BP reduction by the use of diverse ablation systems (Figure 49.5) (41–44). The Symplicity HTN-1 study using a single-electrode radiofrequency catheter reported an office BP decrease by  $-14/-10$ ,  $-21/-10$ ,  $-22/-11$ ,  $-24/-11$ ,  $\kappa\alpha\iota$   $-27/-17$  mmHg after 1, 3, 6, 9, and 12 months (41). The first controlled study of RDN was the Symplicity HTN-2, in which RDN decreased in-office BP by  $32/12$  mmHg and 24-h ambulatory BP by  $11/7$  mmHg at 6 months of follow-up (44). For both trials, longer follow-up of 36 months confirmed the efficacy and safety of the method (41–44). During the same time period the EnligHTN I study using a multi-electrode catheter showed positive data by demonstrating that RDN decreases BP by  $26/10$  mmHg, with 76% of participants to respond to the therapy with a drop of systolic BP  $>10$  mmHg (44).

### THE FIRST SHAM-CONTROLLED TRIAL: SYMPPLICITY HTN-3

In interventional medicine, in order to avoid diverse patient and physician confounders, facilitate blinding and accurately estimate effects of therapy for parameters

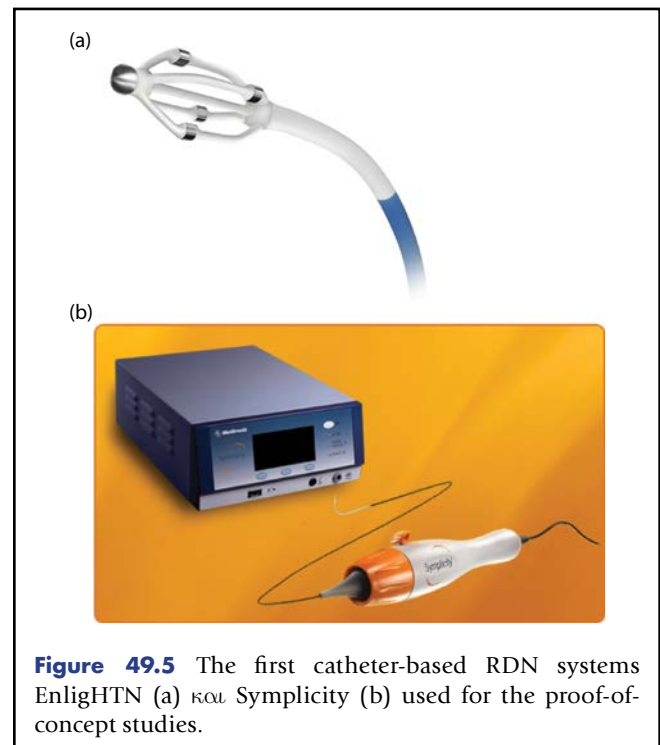


**Figure 49.5** The first catheter-based RDN systems EnligHTN (a)  $\kappa\alpha\iota$  Symplicity (b) used for the proof-of-concept studies.



which are influenced by the 'placebo', the sham-controlled design is proposed. Addressing the abovementioned need, the sham-controlled study in RDN, Symplicity HTN-3 was conducted (45). In the trial 535 patients with resistant hypertension were randomised 2:1 to RDN or sham-RDN. Antihypertensive medication remained stable for at least 2 weeks before the procedure. The primary endpoint of safety was reached, but not efficacy, since the predetermined 5 mmHg cutoff point of difference in office systolic BP between the two arms was not met (45). In the RDN group, systolic BP was reduced by  $-14.1$  mmHg and by  $-11.7$  mmHg in the sham-group. Similarly there was a 2-mmHg difference in the ambulatory BP achieved after 6 months with the patients after RDN presenting a drop of 6.7 mmHg and the sham group a decrease of 4.7 mmHg (45). The frequent and not predefined in terms of drug classes and time-point changes in antihypertensive medication, the relatively small number of ablations performed per patient, the problems of reduced compliance and the great reduction of BP in the sham group are important limitations for Symplicity HTN-3 (46–48). Subsequent analysis revealed that patients with arterial stiffness as reflected by higher pulse pressure were not responders to RDN, and greater reductions in office and ambulatory SBP were observed in those patients with a higher number of ablations and when lesions were created in a four-quadrant pattern (45–48). These findings influenced future sham-controlled studies to include a more structured approach for ensuring compliance, drug intake, titration of therapy and effective ablation by RDN in sham-controlled RDN studies (49).

### OTHER FIRST-GENERATION SHAM-CONTROLLED TRIALS

In the Symplicity HTN-3 aftermath, subsequent sham-controlled smaller trials showed that RDN is at least equally effective to intensive pharmacotherapy in lowering BP in patients with resistant hypertension (50,51). These studies suggested that it is essential to monitor technical success during the intervention and assess compliance to certain medications throughout the studies (50,51). Another most recent sham-controlled trial using external application of ultrasound energy for RDN compared to drug therapy showed no difference in office and ambulatory BP between treatment arms (52).

### STUDIES COMPARING STANDARD STEPWISE PHARMACOLOGICAL THERAPY AND RDN

In the Renal Denervation in Hypertension (DENER-HTN) study, 106 patients with resistant hypertension were randomised to either standard stepwise therapy with predetermined doses of certain drugs (indapamide 1.5 mg, remipril 10 mg or irbesartan 300 mg) and amlodipine 10 mg daily for 4 weeks plus spironolactone 25 mg, bisoprolol 10 mg, prazosine 5 mg and rilmenidine 1 mg (53). There was a  $-5.9$  mmHg difference in the daytime ambulatory BP in the RDN group compared to drug therapy at 6 months. In this well-designed trial, the severity of hypertensive disease was less and baseline BP lower than in the Symplicity HTN-2 study population (43,53).

The Prague-15 study compared RDN with use of the Symplicity catheter ( $n = 52$ ) to intensive pharmacological therapy with spironolactone ( $n = 54$ ) in patients with resistant hypertension. There was a significant reduction of 24-h BP at 6 months  $\pi\pi\pi$  ( $-8.6$  mmHg;  $p < 0.001$  in the RDN compared to  $-8.1$  mmHg,  $p = 0.001$  in the drug group) while there was no significant difference between groups (54). Based on these results, RDN was not superior in BP reduction efficacy but the number of antihypertensive drugs was higher in the group of non-interventional therapy (54). Along the same lines, in the OSLO study with stepwise drug therapy based on the use of the HOTMAN device and strict compliance control it was shown that after 6 months office and ambulatory BP reduction was greater in the non-RDN group, with the limitation of the small number of participants and the use of the impedance system (55).

### CONCLUSIONS AND CONSENSUS FOR THE NEXT RDN TRIALS

After the publication of Symplicity HTN-3, subsequent comprehensive subanalysis of the results along with interesting new preclinical data regarding the location and distribution of renal fibres in the renal arterial wall improved the insight on the potential confounding factors that may explain, at least partially, the unexpected BP responses in both RDN and sham ablation groups as well as the huge variability in BP response post RDN (47,56–59). The list of these confounders includes incomplete denervation, poor antihypertensive medication stability and adherence, selection of non-appropriate population and selection of office BP as endpoint of RDN efficacy (47,56). In addition, pioneer studies have shown that the highest average number of nerves was observed in the proximal and middle segments of the renal artery and the lowest in the distal segments (60,61), while the mean distance from the lumen to the nerve was the longest in the proximal and the lowest in the distal segments. Moreover, reports have suggested that RDN distally in the renal vasculature, and more specifically, in the branches, results in greater noradrenaline reduction (56–61). These points are of importance since they changed our perspective towards RDN trial methodology and overall design, which is reflected to the recent sham-controlled studies.

### SECOND-GENERATION SHAM-CONTROLLED RANDOMISED TRIALS

In order to address the confounders of RDN therapy, three randomised sham-controlled trials have been designed and presented using radiofrequency (SPYRAL HTN-OFF and ON-MED studies) and ultrasound ablation (RADIANCE HTN SOLO) (52,62–63). The SPYRAL HTN-OFF Med and the SPYRAL HTN-ON Med had as primary endpoints the change in 24-h ambulatory blood pressure at 3 months (OFF-MED) and 6 months (ON-Med), while the SPYRAL HTN ON-MED study required patients to be treated with a consistent mono or double- or triple-therapy antihypertensive regimen, whereas the SPYRAL HTN OFF-MED and the RADIANCE HTN SOLO study included drug 'naïve' patients or patients after a 3–4 week drug washout period

(52,62,63). The studies randomise patients with combined systolic-diastolic hypertension (with special attention to exclude isolated hypertension phenotype) to RDN or sham procedure.

The two proof-of-concept SPYRAL HTN studies reported their results at an interim analysis when 80 patients were included (62,63). The SPYRAL trials were proof-of-concept trials to justify larger, powered trial, while the RADIANCE HTN-SOLO trial randomised a total of 146 patients and had the statistical power to detect a difference of 6 mmHg in daytime ambulatory systolic BP between the RDN and the sham group (52). The follow-up phases were at the time-points of 2 months (RADIANCE HTN-SOLO), 3 months (SPYRAL HTN-OFF MED) and 3 and 6 months (SPYRAL HTN-ON MED), respectively. In the three trials,

both patients and physicians remain blinded to randomisation for 6 months at least, and for efficacy and safety the follow-up is extended to 3 years.

In the SPYRAL HTN-OFF MED trial, all patients were off any antihypertensive medication for 4 weeks before randomisation with office BP  $>150/90$  mmHg, and ambulatory BP  $>140$  mmHg systolic (24-h average) (62). A suitable renal artery anatomy and an estimated glomerular filtration rate  $>45$  mL/min/1.73 m<sup>2</sup> was needed. SPYRAL HTN-ON Med included patients with the same BP criteria as in SPYRAL HTN-OFF Med, but one to three antihypertensive medications were allowed (on average 2.2 medications) (62). In the SPYRAL HTN-OFF Med, office BP was 162/100 mmHg and 24-h BP was 152/99 mmHg, and in the SPYRAL HTN-ON Med office BP was 164/101 mmHg and 24-h BP was 151/97 mmHg (62,63).

Regarding the SPYRAL multielectrode catheter (Medtronic, Galway, Ireland) with quadrantic vessel contact, it is an over-the-wire system that uses radiofrequency-energy designed to target the main distal and branch renal arteries with diameter  $>3$  mm by applying energy simultaneously through four electrodes for 60 seconds (Figures 49.6 and 49.7). In both studies, more than 45 ablations were performed per patient (62,63).

In the SPYRAL HTN-OFF Med trial, 24-h ambulatory BP was reduced by 5.5/4.8 mmHg in the RDN group and 0.5/0.4 mmHg in the sham group after 3-month follow-up. The mean baseline-adjusted difference (primary objective) in ambulatory BP between the RDN and the sham groups was  $-4.6/-4.3$  mmHg for 24-h ambulatory BP ( $p = 0.0528/p = 0.0028$ ) in the SPYRAL HTN-OFF Med trial (Figure 49.8) (62). In the SPYRAL HTN-ON Med, 24-h ambulatory BP was reduced in the RDN group by  $-4.8/-4.3$  mmHg after 3 months and  $-9.0/-6.0$  mmHg after 6 months, compared to changes of  $-0.2/-0.6$  mmHg and  $-1.6/-1.9$  mmHg in the sham group, respectively. The mean difference in 24-h ambulatory BP in the SPYRAL HTN-ON Med (6 months) was  $-7.0/-4.3$  mmHg ( $p = 0.0059/0.0174$ ) (Figure 49.9) (63). The mean baseline-adjusted differences

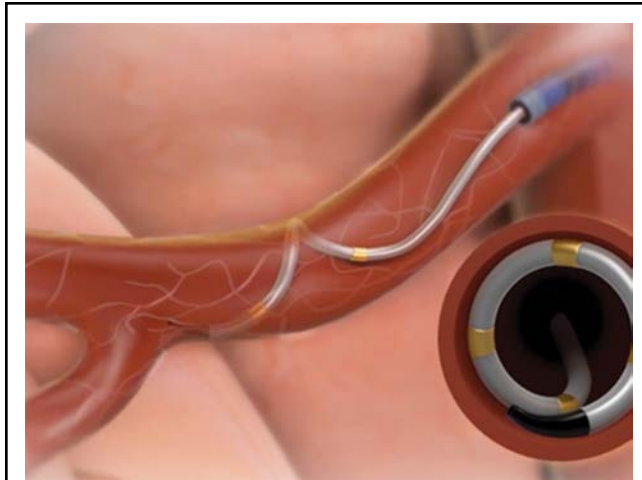


**Figure 49.6** The SPYRAL (Medtronic Inc.) multi-electrode catheter used in the SPYRAL HTN-OFF and HTN-ON MED studies.

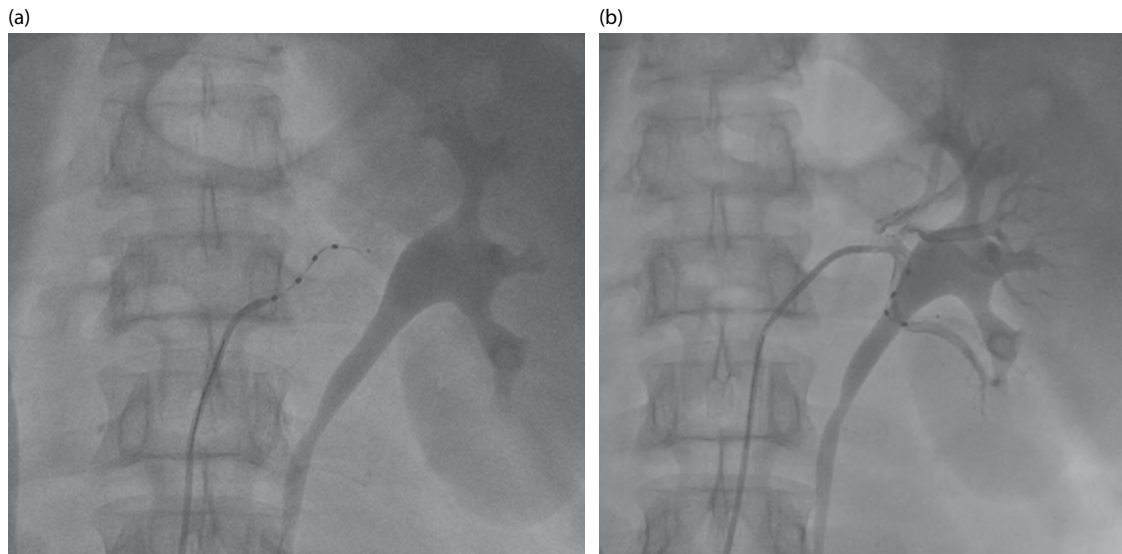


**Figure 49.7** (a) The SPYRAL catheter in the stem of the left main renal artery (Prof. Tsioufis personal archive). (b) The SPYRAL catheter in a branch of the left renal artery (Prof. Tsioufis personal archive).

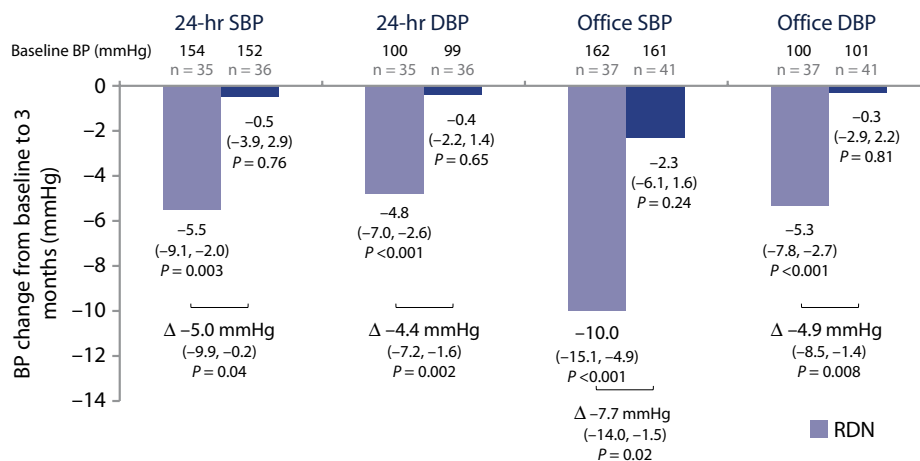


**Figure 49.8** The 3-month results of the SPYRAL HTN-OFF MED sham-controlled trial.

in office BP between the RDN and the sham group were 7.1/–5.0 mmHg ( $p = 0.0212/0.0076$ ) in SPYRAL HTN-OFF Med and –6.6/–4.2 mmHg ( $p = 0.0250/0.0190$ ) in the SPYRAL HTN-ON MED. There was a stable reduction of 24-h BP in the RDN group whereas this was not present in the drug intervention arm, suggesting an ‘always-on’ effect of RDN on BP levels due to the fact that pharmaceutical treatment is influenced by daily action and complicated by intolerances, dosing frequency and levels of adherence (63).

In the SPYRAL HTN-OFF MED study, drug testing was done at baseline and at 3 months to identify whether patients were taking any antihypertensive medications. At baseline, 92.1% (35 of 38) of patients in the renal denervation group and 88.1% (37 of 42) in the sham control group had no evidence of antihypertensive medication use ( $p = 0.72$ ) (62). At 3 months, for available data, 94.3% (33 of 35) of patients in the renal denervation group and 92.7% (38 of 41) in the sham control group had no antihypertensive medications detected ( $p > 0.99$ ) (62). Overall

compliance with the requirement to be off antihypertensive medications at baseline and 3 months was 85.5% (62). In these lines, in the SPYRAL HTN-ON MED study, adherence to antihypertensive drugs was similar between groups and antihypertensive drugs not prescribed by physicians were detected in 10–15% of patients at each time point (63).

Regarding safety, there were no adverse events though the reported follow-up (62,63). This proof-of-concept SPYRAL study provided the evidence for larger pivotal studies with this RDN system.

In the RADIANCE HTN-SOLO, all patients were off antihypertensive medication, and inclusion criteria were office BP  $\geq 140/90$  mmHg and ambulatory BP  $\geq 135/85$  mmHg (daytime) and an estimated glomerular filtration rate  $> 40$  mL/min/1.73 m<sup>2</sup> (63). Baseline office BP was 154/99 mmHg and 24-h BP was 144/88 mmHg (52).

The RADIANCE-HTN trial used a low-pressure water-filled cooling balloon catheter that delivers ultrasound energy to thermally ablate the renal sympathetic nerves

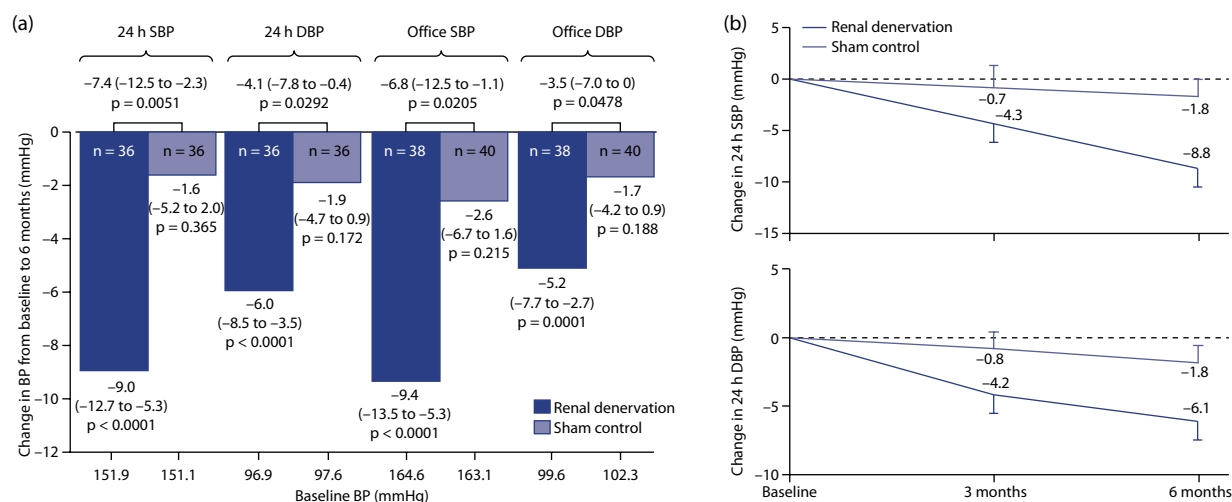
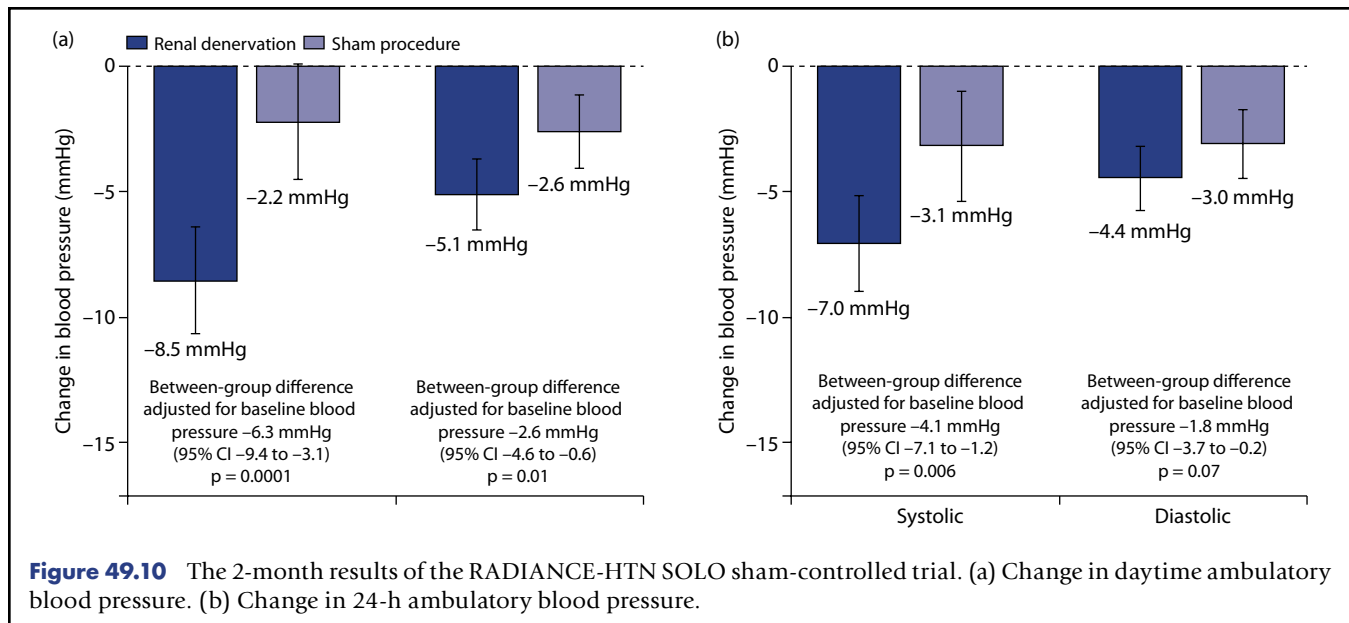


**Figure 49.9** The results of the SPYRAL HTN-ON MED sham-controlled trial. (a) Reduction of 24 hour and office blood pressure in the renal denervation and sham control groups; (b) changes in 24 hour systolic and diastolic blood pressure at 3 and 6 months follow-up.



(Paradise® Renal Denervation System, ReCor Medical, Palo Alto, CA, USA) (52). The system is positioned percutaneously within the main renal artery before the first bifurcation and results in a circumferential ring of ablation (depth of 1–6 mm) (52).

In the RADIANCE SOLO trial, daytime ambulatory BP was reduced by 8.5/5.1 mmHg in the RDN and 2.2/2.6 mmHg in the sham group, and 24-h ambulatory BP was decreased by 7.0/4.4 mmHg in the RDN and 3.1/3.0 mmHg in the sham group (52). The mean baseline-adjusted difference (primary objective) in ambulatory BP (intention to treat population) between the RDN and the sham groups was -6.3/-2.6 mmHg for daytime ambulatory BP ( $p = 0.0001/0.01$ ) and -4.1/-1.8 mmHg for 24-h ambulatory BP ( $p = 0.006/0.07$ ) (Figure 49.10) (52). The mean baseline-adjusted differences in office BP between the RDN and the sham group were -6.5/-4.1 mmHg ( $p = 0.007/0.005$ ).

There were no major adverse events in the RADIANCE HTN-SOLO trial (52). At 6 months, one patient in the RDN underwent renal artery stent placement. For this patient, independent review of their preprocedural and 6-month postprocedure renal artery imaging showed that there was a pre-existing ostial renal artery stenosis (40–50% on MR angiography, 44% on renal angiography), which would have met the criteria for exclusion but was not recognised at the time of randomisation (52).

The results of these second-generation sham-controlled studies provide evidence for effectiveness and safety of RDN therapy in the presence or absence of antihypertensive drugs (52,62,63). The reported reduction of both office and ambulatory BP is consistent throughout these trials and is clinically meaningful in terms of cardiovascular risk reduction. However, further larger scale studies are needed to guide future recommendations for RDN in the therapy of essential hypertension.

## REFERENCES

1. Carlsten A, Folkow B, Grimby G et al. Cardiovascular effects of direct stimulation of the carotid sinus nerve in man. *Acta Physiol Scand* 1958; 44: 138–145.
2. Victor RG. Carotid baroreflex activation therapy for resistant hypertension. *Nat Rev Cardiol* 2015; 12: 451–463.
3. Lohmeier TE, Irwin ED, Rossing MA et al. Prolonged activation of the baroreflex produces sustained hypotension. *Hypertension* 2004; 43(2): 306–311.
4. Illig KA, Levy M, Sanchez L et al. An implantable carotid sinus stimulator for drug-resistant hypertension: Surgical technique and short-term outcome from the multicenter phase II Rheos feasibility trial. *J Vasc Surg* 2006; 44(6): 1213–1218.
5. Scheffers JJ, Kroon AA, Schmidli J et al. Novel baroreflex activation therapy in resistant hypertension: Results of a European multicenter feasibility study. *J Am Coll Cardiol* 2010; 56(15): 1254–1258.
6. Bisognano JD, Bakris G, Nadim MK et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: Results from the double-blind, randomized, placebo-controlled Rheos Pivotal Trial. *J Am Coll Cardiol* 2011; 58(7): 765–773.
7. Bakris GL, Nadim MK, Haller H et al. Baroreflex activation therapy provides durable benefit in patients with resistant hypertension: Results of long-term follow-up in the Rheos Pivotal Trial. *J Am Soc Hypertens* 2012; 6(2): 152–158.
8. de Leeuw PW, Alnima T, Lovett E et al. Bilateral or unilateral stimulation for baroreflex activation therapy. *Hypertension* 2015; 65(1): 187–192.
9. de Leeuw PW, Bisognano JD, Bakris GL et al. Sustained reduction of blood pressure with baroreceptor activation therapy: Results of the 6-year open follow-up. *Hypertension* 2017; 69(5): 836–843.
10. Hoppe UC, Brandt MC, Wachter R et al. Minimally invasive system for baroreflex activation therapy chronically lowers blood pressure with pacemaker-like safety profile: Results from the Barostim neo trial. *J Am Soc Hypertens* 2012; 6(4): 270–276.
11. Wallbach M, Lehnig IY, Schroer C et al. Effects of baroreflex activation therapy on ambulatory blood pressure in patients with resistant hypertension. *Hypertension* 2016; 67(4): 701–709.
12. Spiering W, Williams B, Van der Heyden J et al. Endovascular baroreflex amplification for resistant hypertension: A safety and proof-of-principle clinical study. *Lancet* 2017; 390(10113): 2655–2661.
13. Cooper CB, Celli B. Venous admixture in COPD: Pathophysiology and therapeutic approaches. *COPD* 2008; 5(6): 376–381.
14. Bertog SC, Kolmer C, Kleschnew S et al. Percutaneous femoral arteriovenous shunt creation for advanced chronic obstructive pulmonary disease: A single-center safety and efficacy study. *Circ Cardiovasc Interv* 2012; 5(1): 118–126.
15. Burchell AE, Lobo MD, Sulke N et al. Arteriovenous anastomosis: Is this the way to control hypertension? *Hypertension* 2014; 64(1): 6–12.
16. Saratzis N, Saratzis A, Sarafidis PA et al. Quantitative evaluation of the systemic effects of transposed basilic vein to brachial artery arteriovenous fistula: A prospective study. *J Vasc Access* 2008; 9(4): 285–290.



17. Saxena M, Sobotka PA, Hamshere SM et al. Antihypertensive effects of a central arteriovenous anastomosis are mediated through profound reduction in systemic vascular resistance. *Circ Cardiovasc Interv* 2016; 9(8): e004012.
18. Bertog SC, Sobotka NA, Sobotka PA et al. Percutaneous creation of a central iliac arteriovenous anastomosis for the treatment of arterial hypertension. *Curr Hypertens Rep* 2018; 20(3): 18.
19. Faul J, Schoors D, Brouwers S et al. Creation of an iliac arteriovenous shunt lowers blood pressure in chronic obstructive pulmonary disease patients with hypertension. *J Vasc Surg* 2014; 59(4): 1078–e001083.
20. Lobo MD, Sobotka PA, Stanton A et al. Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): A randomised controlled trial. *Lancet* 2015; 385(9978): 1634–1641.
21. Ott C, Lobo MD, Sobotka PA et al. Effect of arteriovenous anastomosis on blood pressure reduction in patients with isolated systolic hypertension compared with combined hypertension. *J Am Heart Assoc* 2016; 5(12), pii: e004234.
22. Lobo MD, Ott C, Sobotka PA et al. Central iliac arteriovenous anastomosis for uncontrolled hypertension: One-year results from the ROX CONTROL HTN Trial. *Hypertension* 2017; 70(6): 1099–1105.
23. Winter B. Bilateral carotid body resection for asthma and emphysema. A new surgical approach without hypoventilation or baroreceptor dysfunction. *Int Surg* 1972; 57: 458–466.
24. Sinski M, Lewandowski J, Przybylski J et al. Deactivation of carotid body chemoreceptors by hyperoxia decreases blood pressure in hypertensive patients. *Hypertens Res* 2014; 37(9): 858–862.
25. Narkiewicz K, Ratcliffe LE, Hart EC et al. Unilateral carotid body resection in resistant hypertension: A safety and feasibility trial. *JACC Basic Transl Sci* 2016; 1(5): 313–324.
26. Green AL, Wang S, Owen SL et al. Deep brain stimulation can regulate arterial blood pressure in awake humans. *Neuroreport* 2005; 16(16): 1741–1745.
27. Patel NK, Javed S, Khan S et al. Deep brain stimulation relieves refractory hypertension. *Neurology* 2011; 76(4): 405–407.
28. O'Callaghan EL, Hart EC, Sims-Williams H et al. Chronic deep brain stimulation decreases blood pressure and sympathetic nerve activity in a drug- and device-resistant hypertensive patient. *Hypertension* 2017; 69(4): 522–528.
29. Webster M, Valle M, Blake J et al. Median nerve modulation: A novel approach to resistant hypertension. *J Am Soc Hypertens* 2016; 10(4S): e6–e9.
30. Plachta DT, Gierthmuehlen M, Cota O et al. Blood pressure control with selective vagal nerve stimulation and minimal side effects. *J Neural Eng* 2014; 11(3): 036011.
31. Premchand RK, Sharma K, Mittal S et al. Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: Results of the ANTHEM-HF trial. *J Card Fail* 2014; 20(11): 808–816.
32. Antonino D, Teixeira AL, Maia-Lopes PM et al. Non-invasive vagus nerve stimulation acutely improves spontaneous cardiac baroreflex sensitivity in healthy young men: A randomized placebo-controlled trial. *Brain Stimul* 2017; 10(5): 875–881.
33. DiBona GF. Physiology in perspective: The wisdom of the body. Neural control of the kidney based renal sympathetic denervation for resistant hypertension: A multicenter safety and proof-of-principle cohort study. *Lancet* 2005; 373: 1275–1281.
34. Papademetriou V, Tsioufis C, Doumas M. Renal denervation and Symplicity HTN-3: 'Dubium sapientiae initium' (doubt is the beginning of wisdom). *Circ Res* 2014; 115: 211–214.
35. Seravalle G, Dimitriadis K, Dell'Oro R, Grassi G. How to assess sympathetic nervous system activity in clinical practice. *Curr Clin Pharmacol* 2013 Aug; 8(3): 182–188.
36. DiBona GF. Physiology in perspective: The Wisdom of the Body. Neural control of the kidney. *Am J Physiol Regul Integr Comp Physiol* 2005; 289: R633–R641.
37. Schmieder RE, Redon J, Grassi G et al. ESH position paper: Renal denervation - an interventional therapy of resistant hypertension. *J Hypertens* 2012; 30: 837–884.
38. Schiller AM, Pellegrino PR, Zucker IH. The renal nerves in chronic heart failure: Efferent and afferent mechanisms. *Front Physiol* 2015; 6: 224.
39. Grassi G, Seravalle G, Brambilla G et al. Blood pressure responses to renal denervation precede and are independent of the sympathetic and baroreflex effects. *Hypertension* 2015; 65: 1209–1216.
40. Dimitriadis K, Tsioufis C, Tousoulis D. The effect of percutaneous renal denervation on muscle sympathetic nerve activity in hypertensive patients: More questions than answers. *Int J Cardiol* 2014; 176(3): 1382.
41. Krum H, Schlaich M, Whitbourn R et al. Catheter-based renal sympathetic denervation for resistant hypertension: A multicentre safety and proof-of-principle cohort study. *Lancet* 2009; 373: 1275–1281.
42. Investigators SH-1. Catheter-based renal sympathetic denervation for resistant hypertension: Durability of blood pressure reduction out to 24 months. *Hypertension* 2011; 57: 911–917.
43. Esler MD, Krum H, Sobotka PA et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): A randomised controlled trial. *Lancet* 2010; 376: 1903–1909.
44. Worthley SG, Tsioufis CP, Worthley MI et al. Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: The EnligHTN I trial. *Eur Heart J* 2013; 34: 2132–2140.
45. Bhatt DL, Kandzari DE, O'Neill WW et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014; 370: 1393–1401.
46. Lüscher TF, Mahfoud F. Renal nerve ablation after SYMPLICITY HTN-3: Confused at the higher level? *Eur Heart J* 2014; 35: 1706–1711.
47. Mahfoud F, Bhatt DL. Catheter-based renal denervation: The black box procedure. *JACC Cardiovasc Interv* 2013; 6: 1092–1094.
48. Kandzari DE, Bhatt DL, Brar S et al. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. *Eur Heart J* 2015; 36(4): 219–227.
49. Mahfoud F, Schmieder RE, Azizi M et al. Proceedings from the 2nd European Clinical Consensus Conference for device-based therapies for hypertension: State of the art and considerations for the future. *Eur Heart J* 2017; 38: 3272–3281.
50. Mathiassen ON, Vase H, Bech JN et al. Renal denervation in treatment-resistant essential hypertension. A randomized, SHAM-controlled, double-blinded 24-h blood pressure-based trial. *J Hypertens* 2016; 34: 1639–1647.
51. Desch S, Okon T, Heinemann D et al. Randomized sham-controlled trial of renal sympathetic denervation in mild resistant hypertension. *Hypertension* 2015; 65: 1202–1208.
52. Azizi M, Schmieder RE, Mahfoud F et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): A multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet* 2018 9; 391(10137): 2335–2345.
53. Azizi M, Sapoval M, Gosse P et al. Renal Denervation for Hypertension (DENERHTN) investigators. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): A multicentre, open-label, randomised controlled trial. *Lancet* 2015; 385(9981): 1957–1965.
54. Rosa J, Widimský P, Toušek P et al. Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: Six-month results from the Prague-15 study. *Hypertension* 2015; 65: 407–413.
55. FadlElmula FE, Hoffmann P, Larstorp AC et al. Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension. *Hypertension* 2014; 63(5): 991–999.
56. Mahfoud F, Lüscher TF. Renal denervation: Simply trapped by complexity? *Eur Heart J* 2015; 36: 199–202.
57. Tsioufis C, Mahfoud F, Mancia G et al. What the interventionalist should know about renal denervation in hypertensive patients: A position paper by the ESH WG on the interventional treatment of hypertension. *EuroIntervention* 2014; 9: 1027–1035.
58. Tsioufis C, Papademetriou V, Dimitriadis K et al. Catheter-based renal sympathetic denervation exerts acute and chronic effects on renal hemodynamics in swine. *Int J Cardiol* 2013; 168: 987–992.
59. Tsiachris D, Tsioufis C, Dimitriadis K et al. Electrical stimulation of the renal arterial nerves does not unmask the blindness of renal denervation procedure in swine. *Int J Cardiol* 2014; 176: 1061–1063.
60. Henegar JR, Zhang Y, Hata C. Catheter-based radiofrequency renal denervation: Location effects on renal norepinephrine. *Am J Hypertens* 2015; 28: 909–914.
61. Sakakura K, Ladich E, Cheng Q et al. Anatomic assessment of sympathetic peri-arterial renal nerves in man. *J Am Coll Cardiol* 2014; 64: 635–643.
62. Townsend RR, Mahfoud F, Kandzari DE et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): A randomised, sham-controlled, proof-of-concept trial. *Lancet* 2017; 390: 2160–2170.
63. Kandzari DE, Bohm M, Mahfoud F et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet* 2018; 391(10137): 2346–2355.



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## INTRODUCTION

Atrial fibrillation (AF) affects approximately 3% of the world's population, making it the most common cardiac arrhythmia (1–2). The prevalence of AF increases by age (3). Thus, it is obvious that since life expectancy increases, the overall prevalence of AF will grow in the upcoming years (4–5). AF represents a major cause of stroke, heart failure, sudden death and overall mortality (6–8). Many different clinical conditions and risk factors such as arterial hypertension, diabetes mellitus, obesity, metabolic syndrome, coronary heart disease and heart failure are associated with the occurrence of AF. Arterial hypertension (AH) is the most common risk factor, significantly increasing the incidence of cardiovascular events in patients suffering from AF (9). Even high normal blood pressure is associated with increased incidence of AF (10). The prevalence of hypertension appears to be about 30–45% in the general population, with an increasing trend directly related to the ageing population (11). Due to this fact, AH is a leading factor for the development of AF. It is estimated that hypertension raises the risk of AF by about twofold (12). The presence of hypertension increases the incidence of stroke by threefold annually (13–16). The coexistence of hypertension and AF further increases the annual risk of cardiovascular events, and especially stroke. Many of the ischaemic stroke incidents are of unknown origin, with silent AF being a frequent cause. In about one-third of the cases, AF could be subclinical without symptoms (17). In daily practice, the number of patients with AF and AH is growing, and most physicians will regularly need to manage and treat such patients. In this review, we focus on the mechanisms by which AH contributes to the development of AF, as well as the diagnostic and therapeutic approach of these patients beginning from the appropriate blood pressure (BP) measurement in AF patients with AH, and then focussing on the detection and management AF in these patients.

## CORRELATION BETWEEN ARTERIAL HYPERTENSION AND ATRIAL FIBRILLATION: PATHOPHYSIOLOGICAL PATHWAYS

Several scientific data indicate that there is a strong causal link between AH and AF. A 35-year follow-up study which enrolled healthy middle-aged men showed that baseline systolic BP  $\geq 140$  mmHg as well as diastolic BP  $\geq 80$  mm was associated with increased incidence of AF (10). The findings were similar in a large-scale research involving healthy women (18) where 34,221 initially healthy women were followed up for 12.4 years and it was documented that a strong relation between systolic BP (SBP) and diastolic BP (DBP) levels and AF occurrence existed. It is also established that management of BP improves long-term success of AF ablation (19). AH is directly associated with left ventricular hypertrophy (LVH). Increased total peripheral vascular resistance and afterload exert increased wall tension to the left ventricle (LV). Normalisation of wall tensile stress is achieved by an increase in wall thickness (20) according to the Laplace law ( $S = P \times r/h$ , where  $S$  is stress,  $P$  pressure,  $r$  the cavity radius and  $h$  the wall thickness). LV becomes less flexible, and diastolic performance is affected. End diastolic pressure increases and leads to left atrium enlargement which in turn contributes to the appearance and the maintenance of AF (21). It has been shown that AH and LVH activate an increased adrenergic response by the sympathetic nervous system leading to a significant rise in arrhythmic events like AF (21). Moreover, the sympathetic nervous system as well as the renin–angiotensin–aldosterone system is stimulated by the diastolic dysfunction of LV and the resulting increased end-diastolic pressures, contributing to and worsening the arrhythmic procedure (21). A metaanalysis that included 27,141 patients from several studies affirmed that in patients with LVH, supraventricular arrhythmias were

significantly more frequent than in patients without LVH (11.1% vs. 1.1%) (22).

In addition, LVH influences the effectiveness of anticoagulant therapy. In a post hoc analysis, the Randomised Evaluation of Long-term anticoagulation therapy (RE-LY) Study, LVH was associated with lower antithrombotic efficacy of warfarin, but not of dabigatran (23). It also seems that the hypercoagulable state during AF could induce atrial fibrosis and further enhance AF. Spronk et al. (24), in an experimental study, showed that in isolated rat atrial fibroblasts, thrombin enhanced the phosphorylation of the pro-fibrotic signalling molecules Akt and Erk and increased the expression of transforming growth factor  $\beta$ 1 (2.7-fold) and the proinflammatory factor monocyte chemoattractant protein-1 (6.1-fold) by activating protease-activated receptor (PAR)-signalling pathways. They also demonstrated that all effects could be attenuated by the thrombin inhibitor dabigatran. Furthermore, they indicated that in goats with AF, treated with nadroparin targeting the factor Xa-mediated thrombin generation, the complexity of the AF substrate was lower than in control animals, and the arrhythmogenic burden also. Given the fact that novel (new) oral anticoagulants (NOACs) are able to act at the level of both the coagulation cascade and the PAR-signalling pathway (25), unlike vitamin K antagonists (VKAs), it can be said that NOACs may not only prevent strokes but also alter the substrate for AF (24).

Both atrial AF and AH share common risk factors such as smoking, diabetes mellitus, obesity and alcohol consumption, leading to the development of both diseases (29). Thus it is not a surprise that in all recent AF trials, namely RELY, ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), AVERROES (Apixaban versus Acetylsalicylic Acid to Prevent Strokes) and ARISTOTLE (Apixaban for reduction in stroke and other Thromboembolic events in AF), the presence of AH ranged from 49–90% of the individuals with AF (23,26–28), highlighting the fact that AH and AF frequently coexist.

### DIAGNOSIS OF ARTERIAL HYPERTENSION IN PATIENTS WITH ATRIAL FIBRILLATION – BLOOD PRESSURE MEASUREMENT

Several sphygmomanometer types – aneroid, hybrid and the oscillometric – are validated to properly measure BP to assess hypertensive burden and proceed to the therapeutic management of the hypertensive patient (30). Automatic oscillometric devices in particular are useful since they also permit out-of-office BP measurements (home or 24-h ambulatory BP measurements [ABPM]). These devices are programmed to calculate mean BP levels relying on the oscillometric principle and therefore to evaluate SBP and DBP levels by using a specific algorithm (30). However, measurements obtained by automatic oscillometric devices may not be accurate in patients with AF, as they encounter several points assessed as mean arterial pressure. Unfortunately, there are few studies in the literature addressing this issue. According to a meta-analysis (31) that enrolled 566 patients with sustained AF, automated devices (oscillometric or automated Korotkov) appear to be accurate in measuring SBP but not DBP.

In another cross-sectional study (32) that included 102 patients (52 on sinus rhythm, 50 on AF) systolic and diastolic BP did not significantly differ in patients with sinus rhythm and AF, independently of the method of measurement. Although the within-subject variability of the oscillometric measurements was higher in patients with AF compared to those with sinus rhythm, the biases of systolic and diastolic BP did not significantly differ in the presence or absence of AF. A few more studies have assessed the use of ABPM in patients with stable AF. However, the number of participants was small. In these studies, the average of successful BP readings ranged from 80–94% (33–35).

Taking all of this into consideration, we could support the fact that oscillometric devices can be accurate in measuring SBP but not DBP. Since AF is encountered more frequently among the elderly, an age group for which current guidelines recommend BP thresholds only for SBP levels, we may also use these devices for BP measurement in patients with AF, knowing, however, the limitation regarding DBP readings (31,36).

### DETECTION OF ATRIAL FIBRILLATION IN PATIENTS WITH ARTERIAL HYPERTENSION

According to the Framingham Heart Study, the lifetime risk for development of AF is 1 in 4 for men and women 40 years of age and older (37). Based on this finding, the Framingham researchers developed an algorithm to define an individual's absolute risk of developing AF within the next 10 years (38). They used a predictive model relying on risk factors associated with AF occurrence, like SBP.

The early diagnosis of AF is crucial due to the high risk of cardiovascular events in patients with AF. However, in about one-third of the cases, AF can be totally asymptomatic (17,39). In the ALFA Study (40) that enrolled 756 patients with electrocardiographically documented AF, subdivided into paroxysmal (<7 days), chronic (last episode >1 month) and recent onset AF (persistent >7 days and <1 month) symptoms were present only in 88.6% of the patients. More specifically, 16.2% of the participants with permanent AF reported no obvious symptoms, while 5.4% of patients with the paroxysmal form of the arrhythmia were asymptomatic. According to current ESH/ESC guidelines (41), all hypertensive patients should undergo palpation of the pulse at rest to determine heart rate and to search for arrhythmias, especially AF. A 12-lead ECG should be part of the routine tests since it can detect arrhythmias like AF, although this procedure must be carried out by appropriately trained personnel. The Screening for Atrial Fibrillation in the Elderly (SAFE) trial (42) that took place in the UK pointed out that the primary care professionals (general practitioners and practice nurses) could not reliably diagnose AF on an electrocardiogram. Current ESH/ESC guidelines (41) also recommend additional tests in patients with history or physical examination suggestive of arrhythmic events. In case of suspected exercise-induced arrhythmias, a stress ECG test should be considered. However, the existence of AF episodes cannot be ruled out by these tests, since it is not certain that patients will present AF during these diagnostic procedures.

Thus in patients at high risk for the development of AF as well as in patients with cryptogenic stroke, more

extended and reliable AF screening is necessary. Serial ECGs, prolonged ECG monitoring (e.g. for 72 hours or more – ECG Holter monitoring), skin patch recorders for extended continuous ECG monitoring or implantation of loop recorders can enhance the detection of AF (42). Furthermore, oscillometric BP devices with a specific algorithm for the detection of AF may be useful tools in screening for AF at multiple time points during the day. Recently, in a meta-analysis of a total of 2332 individuals with AH, Verberk et al. (43) investigated the use of a specific algorithm for AF detection during automated BP measurement held by oscillometric devices. They concluded that AF detection with routine automated BP measurements is a reliable screening tool in the elderly. They also stated that the accuracy of the procedure depended on the number of the measurements. Thus, taking three sequential readings with at least two detecting AF gave the highest diagnostic accuracy.

Hypertensive patients tend to routinely measure BP levels several times during a day or week. Thus these devices can be a useful tool in revealing arrhythmic events especially in the elderly. Of course, the use of such devices cannot alone be sufficient for the diagnosis of AF, which requires electrocardiographic confirmation (ECG, Holter, etc).

Finally, in patients with rhythm management devices, the interrogation of the device may reveal periods of AF. The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) included 2580 hypertensive patients older than 65 years old, with permanent pacemaker or defibrillator and no history of AF, who were monitored for 3 months in order to detect subclinical atrial tachyarrhythmias. Subclinical atrial tachyarrhythmias had been detected by the pacemaker in 10% of the individuals (44). Moreover, in The Relationship between Daily Atrial Tachyarrhythmia Burden from Implantable Device Diagnostics and Stroke Risk (TRENDS Study), a prospective, observational study that enrolled 3045 patients with  $\geq 1$  stroke risk factor (heart failure, arterial hypertension, age  $\geq 65$  years, diabetes, or prior thromboembolic event) and permanent pacemakers or defibrillators that monitor atrial tachycardia (AT)/AF burden. Patients with longstanding persistent AF or re-entrant supraventricular tachycardias were excluded. During a mean follow-up of 1.4 years, AF was detected in 24% of the individuals (45).

## TREATMENT OF ARTERIAL HYPERTENSION IN PATIENTS WITH ATRIAL FIBRILLATION

AH is major risk factor for stroke. Uncontrolled high BP levels are associated with high risk of ischaemic stroke as well as intracranial bleeding (46–48). The coexistence with AF further increases these risks.

In current ESC guidelines for the management of AF, increased BP levels represent a significant risk factor in the CHA<sub>2</sub>DS<sub>2</sub>-VASc (resting BP  $>140/90$  mmHg) and HASBLED (SBP  $>160$  mmHg) scores predisposing for thromboembolic and haemorrhagic events (40). In the SPORTIF (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation) III and IV trials (49), the researchers investigated the possible connection between

stroke and systemic embolic events (SEE) and the degree of hypertension, in patients with AF, receiving ximelagatran (a direct oral thrombin inhibitor discontinued due to hepatic toxicity). They concluded that event rates markedly increased at SBP levels of  $>$  or  $= 140$ . Likewise, the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial that included 18,201 patients with AF indicated that BP levels  $>140/90$  mmHg at any point during the trial were independently associated with a substantially higher risk of stroke or systemic embolism (SE) (50). Moreover, from a retrospective analysis of the ROCKET AF trial, it has been indicated that the adjusted risk of stroke or SE increased significantly for every 10-mmHg increase in screening SBP (51). Similar findings were collected from a substudy of the RELY trial that included hypertensive patients with AF. Every 10-mmHg increase in mean BP and SBP was associated with an increase by 6–7% in the risk of stroke (52).

Many studies have also indicated the fact that anti-hypertensive treatment is associated with a remarkable reduction in stroke incidence (53), irrespectively of the medication used (46). It has also been indicated that higher BP reduction is related to higher protection against stroke (46). The PROGRESS (The Perindopril Protection against Recurrent Stroke Study) trial, which included patients with a history of a cerebrovascular event, showed that the reduction of SBP from about 165 mmHg to about 115 mmHg was associated with a progressive reduction in the incidence of ischaemic stroke (54). Furthermore, the reduction of SBP by 12–14 mmHg from an initial value of at least 140 mmHg was associated with 70–88% reduction of the risk of intracranial haemorrhagic event. Patients on antithrombotic therapy with an SBP more than 160 mmHg were approximately six times more likely to suffer from intracranial bleeding compared to patients with an SBP of 115 mmHg (55).

Thus, fine BP regulation is a very significant part of the management of AF patients (56). According to current ESC guidelines for the management of AF, it is recommended to use angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) in order to prevent the new onset of AF in patients with AH and cardiac target-organ damage (42). Several studies have indicated the fact that the inhibition of the renin-angiotensin-aldosterone system can be protective regarding structural remodelling of the LV, atrial dilatation and fibrosis, and therefore could prevent AF (57–64). However, these findings have been obtained from retrospective secondary analyses of the trials and concern patients with heart failure or LVH (65–70) only, as these results were not established in patients with AF and no LVH or LV dysfunction (68–69). In conclusion, current ESC guidelines for the management of AF suggest using these drugs in patients with heart failure and reduced ejection fraction as well as in hypertensive patients with LVH.

Moreover, according to the current ESH/ESC guidelines (41), beta-blockers and non-dihydropyridine calcium antagonists are recommended as antihypertensive agents in patients with atrial fibrillation and high ventricular response rates. It is also confirmed by several studies that beta-blockers as well as mineralocorticoid antagonists are effective in preventing the new onset of AF in patients with heart failure and reduced ejection fraction (71,49). Therefore there are many options regarding the drugs that can be used in treating AH in patients with AF. It should

be noted again that the main goal and the main benefit is obtained by controlling BP levels per se.

Finally, it is worth mentioning that excessive reduction of BP may be deleterious. Low on-treatment SBP levels are associated with increased cardiovascular events and all-cause mortality (72). The J-curve phenomenon seems to affect patients with AF. It has been indicated by a post hoc analysis of 3947 participants with AF from the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) trial that BP levels <110/60 mmHg are associated with increased all-cause mortality, as a U-shaped relation existed between BP and all-cause mortality (73).

## CONCLUSION

AF and AH frequently coexist and are both associated with increased risk of stroke. Thus, proper BP measurement and detection of AF are essential in hypertensive patients. Furthermore, existing evidence highlights the great importance of BP control in patients with AF. To achieve this, physicians have all antihypertensive drug classes in their armamentarium. However, the treatment must be individualised, taking into account medical history and comorbidities. This, ultimately, is the art of medicine.

## REFERENCES

- Bjorck S, Palaszewski B, Friberg L, Bergfeldt L. Atrial fibrillation, stroke risk, and warfarin therapy revisited: A population-based study. *Stroke* 2013; 44: 3103–3108.
- Haim M, Hoshen M, Reges O et al. Prospective national study of the prevalence, incidence, management and outcome of a large contemporary cohort of patients with incident non-valvular atrial fibrillation. *J Am Heart Assoc* 2015; 4: e001486.
- Chugh SS, Havmoeller R, Narayanan K et al. Worldwide epidemiology of atrial fibrillation: A Global Burden of Disease 2010 Study. *Circulation* 2014; 129: 837–847.
- Go AS, Hylek EM, Phillips KA et al. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001; 285: 2370–2375.
- Wattigney WA, Mensah GA, Croft JB et al. Increasing trends in hospitalization for atrial fibrillation in the USA, 1985 through 1999; implications for primary prevention. *Circulation* 2003; 108: 711–716.
- Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke* 1991; 22: 983–988.
- Penado S, Cano M, Acha O et al. Atrial fibrillation as a risk factor for stroke recurrence. *Am J Med* 2003; 114: 206–210.
- Benjamin EJ, Wolf PA, D'Agostino RB et al. Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. *Circulation* 1998; 98: 946–952.
- Camm AJ, Kirchhof P, Lip GY et al. Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010; 31: 2369–2429.
- Grundvold I, Skretteberg PT, Liestol K et al. Upper normal blood pressures predict incident atrial fibrillation in healthy middle-aged men: A 35-year follow-up study. *Hypertension* 2012; 59: 198–204.
- Pereira M, Lunet N, Azevedo A, Barros H. Differences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. *J Hypertens* 2009; 27: 963–975.
- Benjamin EJ, Levy D, Vaziri SM et al. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994; 271: 840–844.
- Miller VT, Rothrock JF, Pearce LA et al. Ischemic stroke in patients with atrial fibrillation: Effect of aspirin according to stroke mechanism. *Neurology* 1993; 43: 32–36.
- Investigators SPAF. Risk factors for thromboembolism during aspirin therapy in patients with atrial fibrillation: The Stroke Prevention in Atrial Fibrillation Study. *J Stroke Cerebrovasc Dis* 1995; 5: 147–157.
- Hart RG, Pearce LA, McBride R et al. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: Analysis of 2012 participants in the SPAF I-III Clinical Trials. *Stroke* 1999; 30: 1223–1229.
- Wang TJ, Massaro JM, Levy D et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: The Framingham Heart Study. *JAMA* 2003; 290: 1049–1056.
- Savelieva I, Camm AJ. Silent atrial fibrillation—another Pandora's box. *Pacing Clin Electrophysiol* 2000; 23: 145–148.
- Conen D, Tedrow UB, Koplan BA et al. Influence of systolic and diastolic blood pressure on the risk of incident atrial fibrillation in women. *Circulation* 2009; 119: 2146–2152.
- Pathak RK, Middeldorp ME, Lau DH et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: The ARREST-AF cohort study. *J Am Coll Cardiol* 2014; 64: 2222–2231.
- Mayet J, Hughes A. Cardiac and vascular pathophysiology in hypertension. *Heart* 2003; 89(9): 1104–1109.
- Manolis AJ, Kallistratos MS, Poulimenos LE. Recent clinical trials in atrial fibrillation in hypertensive patients. *Curr Hypertens Rep* 2012; 14: 350–359.
- Chatterjee S, Bavishi C, Sardar P et al. Meta-analysis of left ventricular hypertrophy and sustained arrhythmias. *Am J Cardiol* 2014; 114: 1049–1052.
- Connolly SJ, Ezekowitz MD, Yusuf S et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361: 1139–1151.
- Spronk HMH, De Jong AM, Verheule S et al. Hypercoagulability causes atrial fibrosis and promotes atrial fibrillation. *Eur Heart J* 2017; 38: 38–50.
- Niespialowska-Steuden M, Collins P, Costopoulos C, Gorog DA. NOAC in acute coronary syndrome and AF? *Cardiovasc Hematol Disord Drug Targets* 2014; 14: 154–164.
- Patel MR, Mahaffey KW, Garg J et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365: 883–891.
- Connolly SJ, Eikelboom J, Joyner C et al. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011; 364: 806–817.
- Granger CB, Alexander JH, McMurray JJ et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365: 981–992.
- Vaziri SM, Larson MG, Lauer MS et al. Influence of blood pressure on left atrial size. The Framingham Heart Study. *Hypertension* 1995; 25: 1155–1160.
- Stergiou GS, Parati G, Asmar R et al. Requirements for professional office blood pressure monitors. *J Hypertens* 2012; 30: 537–542.
- Stergiou GS, Kollias A, Destounis A, Tzamouranis D. Automated blood pressure measurement in atrial fibrillation: A systematic review and meta-analysis. *J Hypertens* 2012; 30: 2074–2082.
- Pagonas N, Schmidt S, Eysel J et al. Impact of atrial fibrillation on the accuracy of oscillometric blood pressure monitoring. *Hypertension* 2013; 62: 579–584.
- Stewart MJ, Gough K, Padfield PL. The accuracy of automated blood pressure measuring devices in patients with controlled atrial fibrillation. *J Hypertens* 1995; 13: 297–300.
- Lip GYH, Zarifis J, Beevers M, Beevers DG. Ambulatory blood pressure monitoring in atrial fibrillation. *Am J Cardiol* 1996; 78: 350–353.
- Almeida L, Amado P, Vasconcelos N et al. Is ambulatory blood pressure monitoring reliable in hypertensive patients with atrial fibrillation? *Rev Port Cardiol* 2001; 20: 647–650.
- Parati G, Stergiou G, O'Brien E et al. European Society of Hypertension Working Group on blood pressure monitoring and cardiovascular variability. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. *J Hypertens* 2014; 32: 1359–1366.
- Lloyd-Jones DM, Wang TJ, Leip EP et al. Lifetime risk for development of atrial fibrillation: The Framingham Heart Study. *Circulation* 2004; 110: 1042–1046.
- Schnabel RB, Aspelund T, Li G et al. Validation of an atrial fibrillation risk algorithm in whites and African Americans. *Arch Intern Med* 2010; 170: 1909–1917.
- Furberg CD, Psaty BM, Manolio TA et al. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol* 1994; 74: 236–241.



40. Levy S, Maarek M, Coume LP et al. Characterization of different subsets of atrial fibrillation in general practice in France: The ALFA Study. *Circulation* 1999; 99: 302835.
41. Mancia G, Fagard R, Narkiewicz K et al. Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1281–357.
42. Kirchhof P, Benussi S, Kotecha D et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016; 37: 2893–2962.
43. Verberk WJ, Omboni S, Kollias A, Stergiou GS. Screening for atrial fibrillation with automated blood pressure measurement: Research evidence and practice recommendations. *Int J Cardiol* 2016; 203: 465–473.
44. Healey JS, Connolly SJ, Gold MR et al. ASSERT investigators. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012; 366: 120–129.
45. Glotzer TV, Daoud EG, Wyse DG et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: The TRENDS study. *Circ Arrhythm Electrophysiol* 2009; 2: 474–480.
46. Mancia G, De Backer G, Dominiczak A et al. Guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; 25(6): 1105–1187.
47. Mancia G, Laurent S, Agabiti-Rosei E et al. Reappraisal of European guidelines on hypertension management: A European Society of Hypertension Task Force document. *J Hypertens* 2009; 27(11): 2121–2158.
48. Lewington S, Clarke R, Qizilbash N et al. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360(9349): 1903–1913.
49. Lip GY, Frison L, Grind M; SPORTIF Investigators. Effect of hypertension on anticoagulated patients with atrial fibrillation. *Eur Heart J* 2007; 28: 752–759.
50. Rao MP, Halvorsen S, Wojdyla D et al. Blood pressure control and risk of stroke or systemic embolism in patients with atrial fibrillation: Results from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. *J Am Heart Assoc* 2015; 4: pii: e002015.
51. Vemulapalli S, Hellkamp AS, Jones WS et al. Blood pressure control and stroke or bleeding risk in anticoagulated patients with atrial fibrillation: Results from the ROCKET AF Trial. *Am Heart J* 2016 Aug; 178: 74–84.
52. Nagarakanti R, Wallentin L, Noack H et al. Comparison of characteristics and outcomes of dabigatran versus warfarin in hypertensive patients with atrial fibrillation (from the RE-LY Trial). *Am J Cardiol* 2015; 116: 1204–1209.
53. Collins R, Peto R, MacMahon S et al. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: Overview of randomised drug trials in their epidemiological context. *Lancet* 1990; 335(8693): 827–838.
54. Arima H, Chalmers J, Woodward M et al. Lower target blood pressures are safe and effective for the prevention of recurrent stroke: The PROGRESS trial. *J Hypertens* 2006; 24(6): 1201–1208.
55. Arima H, Anderson C, Omai T et al. Effects of blood pressure lowering on intracranial and extracranial bleeding in patients on antithrombotic therapy: The PROGRESS trial. *Stroke* 2012; 43(6): 1675–1677.
56. Manolis AJ, Rosei EA, Coca A et al. Hypertension and atrial fibrillation: Diagnostic approach, prevention and treatment. Position paper of the Working Group Hypertension Arrhythmias and Thrombosis of the European Society of Hypertension. *J Hypertens* 2012; 30: 239–252.
57. Wachtell K, Lehto M, Gerds E et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared with atenolol: The Losartan Intervention for End Point Reduction in Hypertension (LIFE) study. *J Am Coll Cardiol* 2005; 45: 712–719.
58. Schmieder RE, Kjeldsen SE, Julius S et al. Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: The VALUE trial. *J Hypertens* 2008; 26: 403–411.
59. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; 345: 1667–1675.
60. Vermees E, Tardif JC, Bourassa MG et al. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: Insight from the Studies Of Left Ventricular Dysfunction (SOLVD) trials. *Circulation* 2003; 107: 2926–2931.
61. Ducharme A, Swedberg K, Pfeffer MA et al. Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Am Heart J* 2006; 152: 86–92.
62. Ogunso OA, Shaikh AY, Ahmed M, McManus DD. Atrial fibrillation and hypertension: Mechanistic, epidemiologic, and treatment parallels. *Methodist Debakey Cardiovasc J* 2015; 11(4): 228–234.
63. Yusuf S, Diener HC, Sacco RL et al. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med* 2008; 359: 1225–1237.
64. Schneider MP, Hua TA, Bohm M et al. Prevention of atrial fibrillation by renin-angiotensin system inhibition a meta-analysis. *J Am Coll Cardiol* 2010; 55: 2299–2307.
65. Telmisartan Randomized Assessment Study in ACE intolerant subjects with cardiovascular disease (TRANSCEND) Investigators. Effects of the angiotensin receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: A randomised controlled trial. *Lancet* 2008; 372: 1174–1183.
66. The Active I Investigators. Irbesartan in patients with atrial fibrillation. *N Engl J Med* 2011; 364: 928–938.
67. Tveit A, Grundvold I, Olufsen M et al. Candesartan in the prevention of relapsing atrial fibrillation. *Int J Cardiol* 2007; 120: 85–91.
68. Investigators GISSI-AF, Diertori M, Latini R et al. Valsartan for prevention of recurrent atrial fibrillation. *N Engl J Med* 2009; 360: 1606–1617.
69. Goette A, Schon N, Kirchhof P et al. Angiotensin II-antagonist in paroxysmal atrial fibrillation (ANTIPAF) trial. *Circ Arrhythm Electrophysiol* 2012; 5: 43–51.
70. Nasr IA, Bouzamondo A, Hulot JS et al. Prevention of atrial fibrillation onset by beta-blocker treatment in heart failure: A meta-analysis. *Eur Heart J* 2007; 28: 457–462.
71. Swedberg K, Zannad F, McMurray JJ et al. EMPHASIS-HF Study Investigators. Eplerenone and atrial fibrillation in mild systolic heart failure: Results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) study. *J Am Coll Cardiol* 2012; 59(18): 1598–1603.
72. Kalkman DN, Brouwer TF, Vehmeijer JT et al. The J-curve in patients randomly assigned to different systolic blood pressure targets: An experimental approach to an observational paradigm. *Circulation* 2017; 137(23): 2549–2550.
73. Badheka AO, Patel NJ, Grover PM et al. Optimal blood pressure in patients with atrial fibrillation (from the AFFIRM Trial). *Am J Cardiol* 2014; 114: 727–736.





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# THE DIABETIC/OBESE HYPERTENSIVE PATIENT (INCLUDING METABOLIC SYNDROME)

# 51

Vasilios Kotsis

## INTRODUCTION

### EPIDEMIOLOGY

Modern living in industrialized countries has led to a sedentary lifestyle with limited access to healthy food choices such as fresh fruit and vegetables and increased low-quality high-fat and -carbohydrate diet with enormous food portion sizes. This lifestyle, which includes physical inactivity and atherogenic diet is the leading cause of obesity. Recent data suggest that more than one-third of the US population are obese (1). Type 2 diabetes (T2D), which has closely mirrored obesity statistics, shows increased incidence from 1980 to 2014 for age-adjusted diagnosed diabetes mellitus (DM) from 3.5 to 6.6 per 1000 population. Weight problems and obesity are increasing at a rapid rate in most of the EU member states, with estimates of 51.6% of the EU's population (18 and over) overweight in 2014 (2).

According to the World Health Organization (WHO), there are about 60 million people with diabetes in the European Region, or about 10.3% of men and 9.6% of women aged 25 years and over (3). T2D has spread from industrialized nations to the emerging economies of Asia, Latin America, and Africa. China and India have the largest numbers of individuals with DM (4,5). Regions with the highest prevalence rates of DM are the Pacific Islands and the Middle East, while the regions with the lowest prevalence are South and Central America and Africa (5). Health professionals in the United States had a threefold increased 10-y risk of developing type 2 DM, more than twofold increased 10-y risk for hypertension when overweight, more than 20-fold increased 10-y risk increase for type 2 DM and more than threefold increased 10-y risk for developing hypertension when obese (6).

Obesity is an established risk factor for hypertension (7), and this association is consistent across developing and developed countries (8). Trends in hypertension prevalence rate increased between the third National Health and Nutrition Examination Survey (1988–1994) and the 1999–2004 National Health and Nutrition Examination Survey. Depending on gender and race/ethnicity, from

one-fifth to four-fifths of the increase in hypertension can be accounted for by increasing body mass index (BMI). Hypertension is more than twofold prevalent in obese compared to normal weight individuals (9). Abdominal obesity was also found to be associated with the risk of hypertension independently of BMI (10). The relationship between BMI with mean 24-h daytime and nighttime blood pressure (BP), pulse pressure and heart rate has been confirmed by large studies (11,12). A higher incidence of non-dipping status in obesity was also reported in adults (11).

The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) identified the metabolic syndrome as a multiplex risk factor for cardiovascular disease (CVD) (13). Components of the metabolic syndrome that relate to CVD are abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance and/or glucose intolerance and proinflammatory and prothrombotic state. Criteria of clinical identification of the metabolic syndrome include at least three of these five characteristics: abdominal obesity, given as waist circumference higher than 102 cm in men and 88 cm in women; triglycerides higher than or equal to 150 mg/dL; HDL cholesterol lower than 40 mg/dL in men and 50 mg/dL in women; BP  $\geq 130/85$  mmHg; and fasting glucose  $\geq 110$  mg/d.

### PATHOPHYSIOLOGY OF OBESITY-INDUCED HYPERTENSION AND TYPE II DIABETES

Adipose tissue production of adipokines and cytokines, neurohumoral pathways and metabolic functions contribute to mechanisms that cause hypertension. Obesity-related hypertension may be the result of a combination or overlap of a number of these factors (14). Activation of the sympathetic nervous system (SNS) has been considered to play an important role in the pathogenesis of hypertension among individuals with obesity from impaired function of baroreceptor sensitivity (15), increased levels of circulating free fatty acids (FFAs), increased angiotensin II and actions of insulin and leptin (16). In obesity, primary sodium retention occurs from increased renal tubular reabsorption.

Extracellular fluid volume is expanded, resulting in a hypertensive adjustment of the pressure natriuresis providing a model of hypertension due to volume overload (17). Increased plasma renin activity (PRA), plasma angiotensinogen, angiotensin II and aldosterone levels have been reported in obesity (18). Renin–angiotensin system (RAS) has a regulatory mechanism from preventing extreme variations in arterial pressure caused from changes in salt intake and determines obesity-related BP as a salt-sensitive condition (19). Obesity is accompanied by high levels of circulating insulin and reduced sensitivity to the metabolic actions of insulin. Insulin exhibits a sodium-retaining effect through its direct action on the renal tubules, and chronic hyperinsulinemia has been associated with vasoconstriction (20). Insulin resistance also down-regulates nitric oxide (NO) synthesis and increases vascular and systemic inflammation (21) that can cause endothelial dysfunction. Biologically active derivatives generate from adipose cells, including reactive oxygen species, proinflammatory and inflammatory molecules (interleukin-1 $\beta$  [IL-1], interleukin-6 [IL-6], tumour necrosis factor- $\alpha$  [TNF $\alpha$ ], C-reactive protein [CRP]) and angiogenic factors (vascular endothelial growth factor [VEGF]) promote vascular damage, endothelial dysfunction and hypertension (22). The intestinal microbiota and changes in intestinal permeability have been reported as potential triggers of inflammation in obesity (14,23).

Genome-wide association studies have established more than 175 common variants for type 2 DM and obesity, but with little shared genetic aetiology accounting only for 15/20% of known heritability (24). Genetic susceptibility to type 2 DM is mediated through effects on both insulin release and insulin sensitivity. Epigenetic effects seem to have an important role impairing  $\beta$ -cell function, and BMI is more predictive of diabetes than any of the common risk alleles identified by genome-wide association studies. Lifestyle factors such as chemical exposures, diet, physical activity and age can also affect gene expression (25). Type 2 DM combines a progressive defect in insulin action (insulin resistance) and insulin secretion

( $\beta$ -cell failure) that has been decline more than 50% of normal at diagnosis. Excessive deposition of fat within the visceral adipose tissue and ectopic fat within muscle, liver and pancreas impair these organ functions (26). Adipocytes are an active endocrine organ that secretes numerous inflammatory cytokines that can have paracrine and systemic hormonal effects and lower levels of protective anti-inflammatory adipocytokines such as adiponectin (27). Increased secretion of TNF $\alpha$ , interleukins, plasminogen activator inhibitor-1, and retinol-binding protein-4 and secretion of macrophage chemoattractant protein-1 (MCP-1) drives macrophage infiltration of adipose tissue (28). Insulin has antilipolytic effects by suppressing lipase activity within adipose tissue. Insulin resistance increases output of FFAs into the circulation for ectopic uptake, predominantly by liver and muscle. The liver stores excessive fat that causes hepatic steatosis and subsequent nonalcoholic fatty liver disease (NAFLD) (29). Increased FFA secretion from adipose tissue may exceed the liver's capacity to synthesize triglycerides, leading to diacylglyceride (DAG) formation. Failure of hepatic glucose output to suppress both fasting and after meals is the hallmark of metabolic disturbance in type 2 DM resulting in hyperglycaemia. Similar inflammatory processes take place within the pancreas in obesity and drive  $\beta$ -cell apoptosis and dysfunction (30).

## DEFINITION OF HYPERTENSION IN DIABETES

The definition of hypertension in diabetes differs between societies, but the most common definition is BP values higher than 130 mmHg for systolic and 80 for diastolic (Figure 51.1) (31,32), and J-curve is unlikely to occur until these BP values, except for very aged populations that have important vascular damage (33). The diabetic patient should have orthostatic BP measured (34), as the coexistence of diabetic neuropathy may exaggerate orthostatic hypotension. In obesity, the definition of hypertension is BP greater than 140/90 mmHg.

**Guidelines for management of hypertension in the diabetic hypertensive patient**

| Organization                  | Year | Systolic BP | Diastolic BP |
|-------------------------------|------|-------------|--------------|
| AHA                           | 2017 | <130        | <80          |
| ADA                           | 2017 | <140        | <80          |
| Canadian Hypertension Society | 2016 | <130        | <80          |
| JNC VIII                      | 2015 | <140        | <90          |
| American Diabetes Association | 2007 | <130        | <80          |
| ESH/ESC                       | 2013 | <140        | <85          |
| NICE                          | 2008 | <130        | <80          |
| American Diabetes Association | 2007 | <130        | <80          |
| British Hypertension Society  | 2004 | <130        | <80          |
| ESH/ESC                       | 2003 | <130        | <80          |
| JNC VII                       | 2003 | <130        | <80          |
| National Kidney Foundation    | 2000 | <130        | <80          |
| Canadian Hypertension Society | 1999 | <130        | <80          |
| British Hypertension Society  | 1999 | <140        | <80          |
| WHO/ISH                       | 1999 | <130        | <85          |
| JNC VI                        | 1997 | <130        | <85          |

**Figure 51.1** Definition of hypertension in different guidelines in the diabetic patient.

Diagnosis of hypertension should be done with the correct cuff size (large adult or extra-large) because of the increased circumference of the obese subject's arm (35). This cuff size should also be used for out-of-office BP measurements (home BP measurements or ambulatory BP monitoring) for correct measurements (31). Out-of-office BP is important in the diagnosis of obesity-induced hypertension because white-coat hypertension is highly prevalent in obese subjects (11).

## TARGET-ORGAN DAMAGE IN DIABETES/OBESITY

### HEART AND VESSELS

Obesity increases blood volume and cardiac output, leading to excess venous return to heart. Shear stress dilates left and right ventricle walls and eventually reduces left ventricular pump strength. Obesity-induced hypertension may also in part explain the development of left ventricular hypertrophy (36). Atherosclerosis, lipotoxicity and endothelial dysfunction promote coronary artery disease (CAD) and myocardial infarction. Myocardial fibrosis and atherosclerosis can be accelerated by insulin resistance and adipokine release in both obesity and diabetes. Obesity increases the risk of heart failure (37,38). Obesity is also an independent risk factor for the development of atrial fibrillation (39,40). The MADIT-II study shows that a BMI >30 kg/m<sup>2</sup> is an independent risk factor for ventricular tachyarrhythmias, and obesity and diabetes are associated with an increased risk of sudden cardiac death (41). Conditions that may trigger cardiac fibrosis are the upregulation of the renin angiotensin system, transforming growth factor (TGF)- $\beta$ , endothelin, leptin and other inflammatory mediators. Insulin resistance contributes to left ventricular hypertrophy, and abdominal fat distribution increases the adrenergic tone and altered reflex control mechanisms contributing to cardiac work and to increased ventricular arrhythmia susceptibility (39). Obstructed sleep apnoea is a condition characterized by hypoxaemia, hypercapnia, reoxygenation, sleep deprivation, alteration in intrathoracic pressure and arousal. The pathophysiological results of this condition include sympathetic activation, metabolic dysregulation, endothelial dysfunction, systemic inflammation, hypercoagulability and left atrial enlargement that increase the risk of atrial fibrillation, stroke and sudden cardiac death (42). Finally, obesity and diabetes increase the risk of stroke from accelerating atherosclerosis and/or thromboembolism that may result in arterial occlusion or rupture. Electrocardiogram (ECG) may detect CAD, left ventricular hypertrophy and arrhythmias, but echocardiography is more sensitive in the diagnosis of left ventricular hypertrophy. Other exams that might be performed in patients with diabetes, obesity and hypertension are stress ECG or echo and 24-h Holter ECG to detect possible CAD or arrhythmias. Obesity is also associated with increased arterial stiffness (43), increased carotid artery intima media thickness (44,45), flow-mediated dilation and early vascular ageing (46).

### KIDNEYS

Diabetes mellitus and hypertension are independent factors for chronic kidney disease (CKD). A large European

cohort reported that obesity per se is also one of the strongest risk factors for new onset of CKD (47). Kidney impairment in obesity starts with glomerular hyperfiltration, which is observed before the appearance of glomerulomegaly or renal dysfunction; thus it could be considered an early marker of obesity-related kidney disease. The primary histologic features in obesity are relatively few lesions of focal-segmental glomerulosclerosis, profound glomerulomegaly due to glomerular hyalinosis and fibrosis, as well as lipid accumulation in the glomeruli and adhesion to Bowman's capsule (16). Diabetic nephropathy starts with glomerular basement membrane thickening followed by mesangial expansion, nodular sclerosis and finally glomerulosclerosis. In clinical praxis diabetic nephropathy can be detected either as increased e-GFR or microalbuminuria in the early stages of the disease, followed by proteinuria that can reach the nephrotic syndrome values and reduction in e-GFR hypofiltration leading to end-stage renal disease (ESRD). Obesity, hypertension and diabetes are the most common causes of ESRD in Western countries (48).

## TREATMENT OF HYPERTENSION IN THE DIABETIC/OBESE PATIENT

### LIFESTYLE MODIFICATION

#### WEIGHT MANAGEMENT

Lifestyle interventions constitute behavioural modifications and hypocaloric diets. Behavioural therapy is based on self-monitoring of food intake, increased physical activity, stimulus control, problem solving and relapse prevention. Studies have shown that self-monitoring of food intake and weekly measurement of body weight are important factors of short- and long-term weight loss (49). Although these interventions are commonly recommended in patients with obesity, diabetes and hypertension, average weight loss is modest, and most patients regain weight within months to a few years. The Mediterranean diet is known for its beneficial metabolic effects and for its ability to delay need for drug therapy in newly diagnosed type 2 DM patients (50). Energy-restricted diets have beneficial effects on reducing hypertension, dyslipidemia and type 2 DM. Very-low-energy diet can be useful to reduce total cardiovascular risk and T2D. Such diets may reverse type 2 DM, as reported in the DIRECT trial that used a very low caloric diet (825–853 kcal/day formula diet for 3–5 months), followed by stepped food reintroduction for 2–8 weeks and structured support for long-term weight loss maintenance (51). This intervention resulted in achieving remission to a nondiabetic state in half of the study population, and patients were off antidiabetic drugs the next year. A modest weight loss of 5–10% seems to be necessary to reduce haemoglobin A1c (HbA1c) levels and decrease the use of hyperglycaemic-, hypertension- and lipid-lowering medications as observed after 1 year in the Look AHEAD study (52). Diet choice should always be based on the patient's individual food preferences, lifestyle and medical condition to ensure sustained diet adherence.

### PHYSICAL ACTIVITY AND CARDIORESPIRATORY FITNESS

Physical activity alone has only a moderate effect on weight loss, while guidelines recommend at least 150 min/week

of moderate aerobic exercise in combination with three weekly sessions of resistance training to increase muscle strength (53). Cardiorespiratory fitness (CRF) assesses the functional capacity of an individual is measured as maximal oxygen consumption ( $\text{VO}_2\text{max}$ ), estimated from the peak work rate achieved on a treadmill, and is a strong and independent marker of cardiovascular risk (39). Obesity with low CRF is associated with increased CV risk factors such as hypertension and diabetes. The 'fat-and-fit' concept may reclassify obese subjects' individual CV risk (54), suggesting that overweight but not fit may have higher risk than obese but fit patients.

## PHARMACOLOGICAL TREATMENT FOR OBESITY AND HYPERTENSION

Antiobesity agents are recommended for patients with obesity-related comorbidity (e.g. hypertension, type 2 DM with a BMI at least  $27 \text{ kg/m}^2$ ) (30,53,55). In Europe, orlistat and liraglutide 3 mg licensed for obesity may have some beneficial effects on hypertension. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and long-acting calcium channel blockers (CCBs) are preferred (30). These drug classes have neutral effect on weight gain. RAS inhibition may also have beneficial effects on glucose metabolism and may prevent progression to type 2 DM, and CCBs have at least a neutral effect on glucose metabolism. Thiazide-like diuretics may worsen glucose metabolism and their use may be appropriate when other combinations fail. Mineralocorticoid receptor antagonists may be used in resistant obese hypertensives (35). Treatment with beta-blockers promotes weight gain, limiting their utility in the treatment of patients with obesity except for the absolute indications (heart failure with reduced ejection fraction or secondary

prevention after coronary heart disease). Newer vasodilating beta-blockers may have attenuated effects on insulin sensitivity.

## PHARMACOLOGICAL TREATMENT FOR OBESITY, HYPERTENSION AND DIABETES MELLITUS

Antiobesity agents have shown to help patients with type 2 DM to achieve weight-loss goals and to improve Hb1Ac-levels. Targeting obesity can improve glycaemic control and should represent the first approach in the management of type 2 DM. The primary focus of diabetes management is the prevention of additional weight gain. Most of the traditional antidiabetic drugs promote weight gain and make the task of successful management of overweight or obese individuals with T2D a challenging task. Metformin and dipeptidyl peptidase-IV (DPP-IV) inhibitors are weight-neutral glucose-lowering drugs (30). Newer glucose-lowering agents, including sodium-glucose cotransporter 2 (SGLT2)-inhibitors and GLP1-analogues, support weight loss and should be the preferred choice of treatment for obese type 2 DM individuals. In patients with type 2 DM and hypertension, empagliflozin (56), canagliflozin (57) and dapagliflozin (58) reduced body weight and BP versus placebo, irrespective of the use of other antihypertensive drugs. Liraglutide and dulaglutide, GLP1 receptor analogues tested in patients with type 2 DM and high cardiovascular risk reduced body weight and SBP but increased DBP and heart rate compared to placebo. Empagliflozin (59), canagliflozin (57) and liraglutide (60) reduced CV risk in patients with type 2 diabetes mellitus. Combining exenatide with dapagliflozin was superior to either drug alone for weight loss and SBP reduction (61) (Figures 51.2 and 51.3).

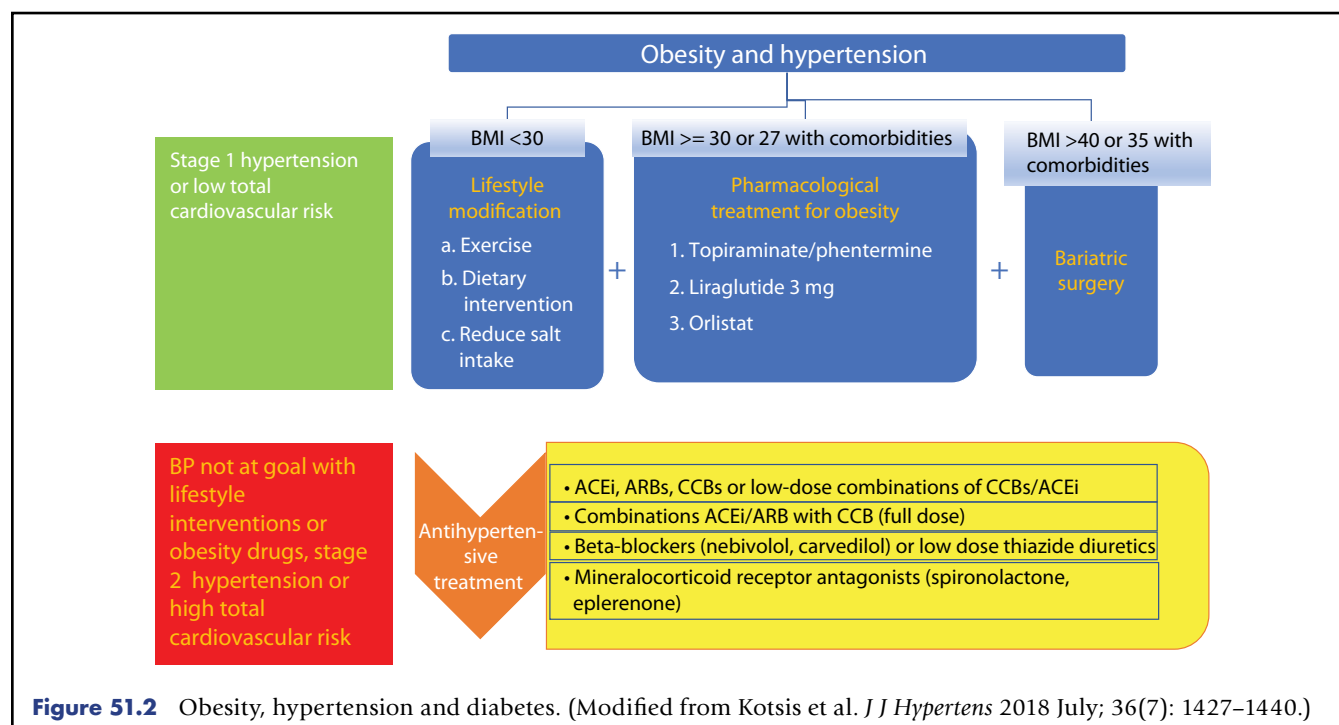
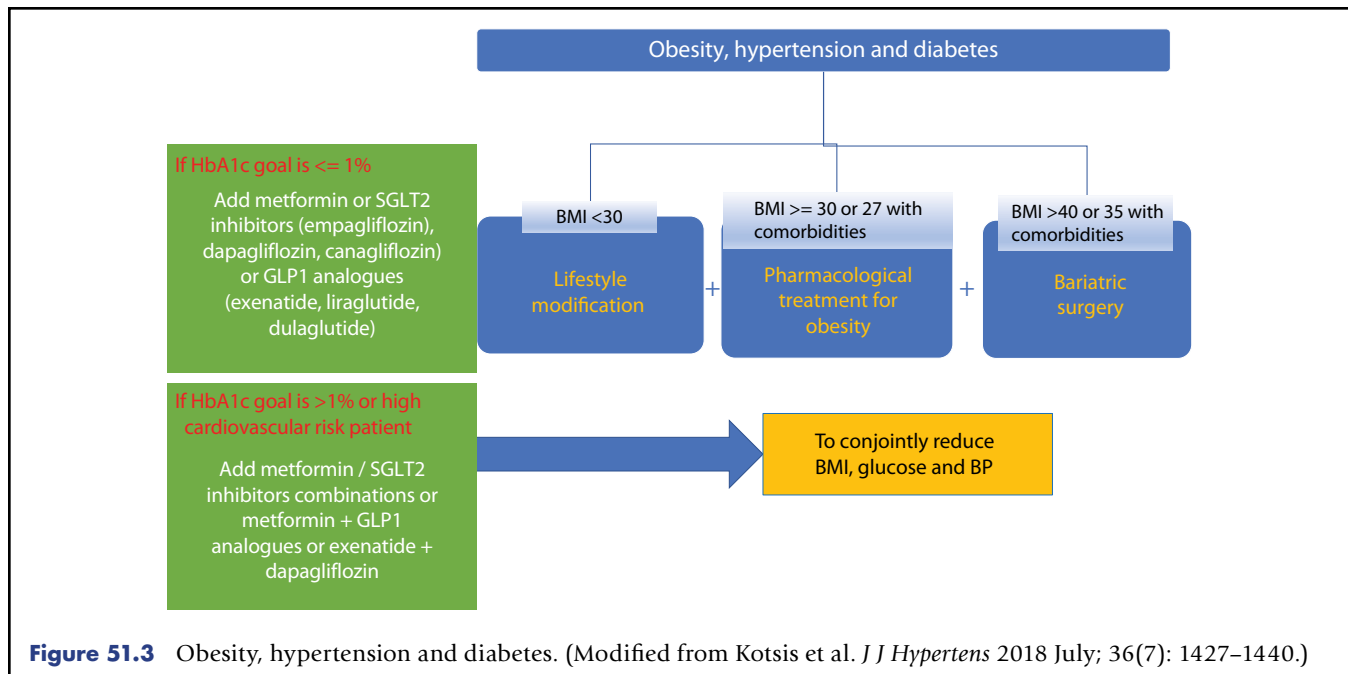


**Figure 51.2** Obesity, hypertension and diabetes. (Modified from Kotsis et al. *J J Hypertens* 2018 July; 36(7): 1427–1440.)





## BARIATRIC (METABOLIC) SURGERY

Bariatric surgery is effective for long-term weight loss for overt obesity (62). It is recommended for individuals aged 18–60 years with a BMI  $\geq 40$  kg/m<sup>2</sup>, or for patients with a BMI  $\geq 35$  kg/m<sup>2</sup> and obesity-related comorbidities, such as type 2 DM and hypertension. Bariatric surgery reduces 15–40% the body weight, improving type 2 DM and hypertension. Of the weight loss, 20–25% may be regained over a period of 10 years after the intervention. Bariatric surgery is superior to other interventions in achieving long-term sustained weight loss in morbidly obese patients and is associated with improvement in glucose metabolism and sometimes in DM remission, with remission rates varying between 45–95% depending on the type of procedure (63). Type 2 DM recurrence or worsening in patients with initial resolution or improvement can be observed after years, as shown by the follow-up report of the SOS trial, where 50% of the patients who underwent surgery with remission of DM at 2 years relapsed after 10 years. DM relapse was associated with less initial weight loss and greater weight regain (64).

## TREATMENT OF OTHER RISK FACTORS

Atherogenic dyslipidemia is one of the major risk factors for CV disease in people with type 2 DM. Dyslipidemia in obesity is a cluster of lipid and lipoprotein abnormalities with elevated triglycerides, apoB and small dense LDL combined with low HDL and apoA1. The primary target of hypolipidemic treatment is the reduction of LDL levels with lifestyle interventions, weight loss treatment and the use of statins and ezetimibe (30). In high-risk obese patients with serum triglycerides  $> 2.5$  mmol/L (especially in those with simultaneously low HDL cholesterol levels) despite appropriate well-tolerated statin therapy, fenofibrate can be used in combination with statins. Statin

treatment is associated with body weight gain and drug-induced new-onset DM, but these effects are minor when compared to life that will be saved with stain treatment from CV disease.

## REFERENCES

1. Bhupathiraju SN, Hu FB. Epidemiology of obesity and diabetes and their cardiovascular complications. *Circ Res* 2016; 118(11): 1723–1735.
2. [http://ec.europa.eu/eurostat/statistics-explained/index.php/Overweight\\_and\\_obesity\\_-\\_BMI\\_statistics](http://ec.europa.eu/eurostat/statistics-explained/index.php/Overweight_and_obesity_-_BMI_statistics). Accessed on 23 March 2019.
3. <http://www.euro.who.int/en/health-topics/noncommunicable-diseases/diabetes/data-and-statistics>. Accessed on 23 March 2019.
4. Unnikrishnan R, Pradeepa R, Joshi SR, Mohan V. Type 2 diabetes: Demystifying the global epidemic. *Diabetes* 2017; 66(6): 1432–1442.
5. <https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/134-idf-diabetes-atlas-8th-edition.html>. Accessed on 23 March 2019.
6. Field AE, Coakley EH, Must A et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Arch Intern Med* 2001; 161(13): 1581–1586.
7. Garrison RJ, Kannel WB, Stokes J, 3rd, Castelli WP. Incidence and precursors of hypertension in young adults: The Framingham offspring study. *Prev Med* 1987; 16(2): 235–251.
8. Doll S, Paccaud F, Bovet P et al. Body mass index, abdominal adiposity and blood pressure: Consistency of their association across developing and developed countries. *Int J Obes Relat Metab Disord* 2002; 26(1): 48–57.
9. Cutler JA, Sorlie PD, Wolz M et al. Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988–1994 and 1999–2004. *Hypertension* 2008; 52(5): 818–827.
10. Seven E, Thuesen BH, Linneberg A, Jeppesen JL. Abdominal adiposity distribution quantified by ultrasound imaging and incident hypertension in a general population. *Hypertension* 2016; 68(5): 1115–1122.
11. Kotsis V, Stabouli S, Bouldin M et al. Impact of obesity on 24-hour ambulatory blood pressure and hypertension. *Hypertension* 2005; 45(4): 602–607.
12. Stabouli S, Kotsis V, Papamichael C et al. Adolescent obesity is associated with high ambulatory blood pressure and increased carotid intimal-medial thickness. *J Pediatr* 2005; 147(5): 651–656.
13. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment

- of High Blood Cholesterol in Adults (Adult Treatment Panel III). Final Report. *Circulation* 2002; 106(25): 3143–3421.
14. Kotsis V, Nilsson P, Grassi G et al. New developments in the pathogenesis of obesity-induced hypertension. *J Hypertens* 2015; 33(8): 1499–1508.
  15. Grassi G, Seravalle G, Cattaneo BM et al. Sympathetic activation in obese normotensive subjects. *Hypertension* 1995; 25(4 Pt 1): 560–563.
  16. Kotsis V, Stabouli S, Papakatsika S et al. Mechanisms of obesity-induced hypertension. *Hypertens Res* 2010; 33(5): 386–393.
  17. Young DB, McCaa RE, Pan YJ, Guyton AC. The natriuretic and hypotensive effects of potassium. *Circ Res* 1976; 38(6 Suppl 2): 84–89.
  18. Underwood PC, Adler GK. The renin angiotensin aldosterone system and insulin resistance in humans. *Curr Hypertens Rep* 2013; 15(1): 59–70.
  19. Bailey MA. 11 $\beta$ -Hydroxysteroid dehydrogenases and hypertension in the metabolic syndrome. *Curr Hypertens Rep* 2017; 19(12): 100.
  20. Mahmoud AM, Szczurek MR, Blackburn BK et al. Hyperinsulinemia augments endothelin-1 protein expression and impairs vasodilation of human skeletal muscle arterioles. *Physiol Rep* 2016; 4:16.
  21. Cox AJ, West NP, Cripps AW. Obesity, inflammation, and the gut microbiota. *Lancet Diabetes Endocrinol* 2015; 3(3): 207–115.
  22. Steven S, Dib M, Hausding M et al. CD40L controls obesity-associated vascular inflammation, oxidative stress, and endothelial dysfunction in high fat diet-treated and db/db mice. *Cardiovasc Res* 2018; 114(2): 312–323.
  23. Antza C, Stabouli S, Kotsis V. Gut microbiota in kidney disease and hypertension. *Pharmacol Res* 2018; 130: 198–203.
  24. Karaderi T, Drong AW, Lindgren CM. Insights into the genetic susceptibility to type 2 diabetes from genome-wide association studies of obesity-related traits. *Curr Diab Rep* 2015; 15(10): 83.
  25. Bernstein D, Golson ML, Kaestner KH. Epigenetic control of beta-cell function and failure. *Diabetes Res Clin Pract* 2017; 123: 24–36.
  26. Shimabukuro M, Kozuka C, Taira S et al. Ectopic fat deposition and global cardiometabolic risk: New paradigm in cardiovascular medicine. *J Med Invest* 2013; 60(1–2): 1–14.
  27. Jung DH, Kim JY, Kim JK et al. Relative contribution of obesity and serum adiponectin to the development of hypertension. *Diabetes Res Clin Pract* 2014; 103(1): 51–56.
  28. Cusi K. The role of adipose tissue and lipotoxicity in the pathogenesis of type 2 diabetes. *Curr Diab Rep* 2010; 10(4): 306–315.
  29. Meex RCR, Watt MJ. Hepatokines: Linking nonalcoholic fatty liver disease and insulin resistance. *Nat Rev Endocrinol* 2017; 13(9): 509–520.
  30. Kotsis V, Jordan J, Micic D et al. Obesity and cardiovascular risk: A call for action from the European Society of Hypertension Working Group of Obesity, Diabetes and the High-risk Patient and European Association for the Study of Obesity: Part A: Mechanisms of obesity induced hypertension, diabetes and dyslipidemia and practice guidelines for treatment. *J Hypertens* 2018; 36(7): 1427–1440.
  31. Stergiou GS, Parati G, Vlachopoulos C et al. Methodology and technology for peripheral and central blood pressure and blood pressure variability measurement: Current status and future directions. Position statement of the European Society of Hypertension Working Group on blood pressure monitoring and cardiovascular variability. *J Hypertens* 2016; 34(9): 1665–1677.
  32. Antza C, Doundoulakis I, Stabouli S, Kotsis V. Comparison among recommendations for the management of arterial hypertension issued by last US, Canadian, British and European guidelines. *High Blood Press Cardiovasc Prev* 2018; 25(1): 9–16.
  33. Whelton PK, Carey RM, Aronow WS et al. ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018; 71(19): e127–e248.
  34. Costa A, Bosone D, Ramusino MC et al. Twenty-four-hour blood pressure profile, orthostatic hypotension, and cardiac dysautonomia in elderly type 2 diabetic hypertensive patients. *Clin Auton Res* 2016; 26(6): 433–439.
  35. Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension. *Blood Press* 2014; 23(1): 3–16.
  36. Kotsis V, Stabouli S, Toumanidis S et al. Obesity and daytime pulse pressure are predictors of left ventricular hypertrophy in true normotensive individuals. *J Hypertens* 2010; 28(5): 1065–1073.
  37. Jordan J, Toplak H, Grassi G et al. Joint statement of the European Association for the Study of Obesity and the European Society of Hypertension: Obesity and heart failure. *J Hypertens* 2016; 34(9): 1678–1688.
  38. Alpert MA, Lavie CJ, Agrawal H et al. Obesity and heart failure: Epidemiology, pathophysiology, clinical manifestations, and management. *Transl Res* 2014; 164(4): 345–356.
  39. Kotsis V, Tsioufis K, Antza C et al. Obesity and cardiovascular risk: A call for action from the European Society of Hypertension Working Group of Obesity, Diabetes and the High-risk Patient and European Association for the Study of Obesity: Part B: Obesity-induced cardiovascular disease, early prevention strategies and future research directions. *J Hypertens* 2018 July; 36(7): 1441–1455.
  40. Heckbert SR, Wiggins KL, Blackshear C et al. Pericardial fat volume and incident atrial fibrillation in the Multi-Ethnic Study of Atherosclerosis and Jackson Heart Study. *Obesity (Silver Spring)* 2017; 25(6): 1115–1121.
  41. Pietrasik G, Goldenberg I, McNitt S et al. Obesity as a risk factor for sustained ventricular tachyarrhythmias in MADIT II patients. *J Cardiovasc Electrophysiol* 2007; 18(2): 181–184.
  42. Linz D, McEvoy RD, Cowie MR et al. Associations of obstructive sleep apnea with atrial fibrillation and continuous positive airway pressure treatment: A review. *JAMA Cardiol* 2018; 3(6): 532–540.
  43. Nilsson PM, Boutouyrie P, Cunha P et al. Early vascular ageing in translation: From laboratory investigations to clinical applications in cardiovascular prevention. *J Hypertens* 2013; 31(8): 1517–1526.
  44. Kotsis VT, Stabouli SV, Papamichael CM, Zakopoulos NA. Impact of obesity in intima media thickness of carotid arteries. *Obesity (Silver Spring)* 2006; 14(10): 1708–1715.
  45. Stabouli S, Kotsis V, Karagianni C et al. Blood pressure and carotid artery intima-media thickness in children and adolescents: The role of obesity. *Hellenic J Cardiol* 2012; 53(1): 41–47.
  46. Jordan J, Nilsson PM, Kotsis V et al. Joint scientific statement of the European Association for the Study of Obesity and the European Society of Hypertension: Obesity and early vascular ageing. *J Hypertens* 2015; 33(3): 425–434.
  47. Obermayr RP, Temml C, Knechtelsdorfer M et al. Predictors of new-onset decline in kidney function in a general Middle-European population. *Nephrol Dial Transplant* 2008; 23(4): 1265–1273.
  48. USRDS U. Annual data report: Atlas of chronic kidney disease and end-stage renal disease in the United States. *NIDDK* 2013.
  49. Akers JD, Cornett RA, Savla JS et al. Daily self-monitoring of body weight, step count, fruit/vegetable intake, and water consumption: A feasible and effective long-term weight loss maintenance approach. *J Acad Nutr Diet* 2012; 112(5): 685–692, e2.
  50. Esposito K, Maiorino MI, Ciotola M et al. Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: A randomized trial. *Ann Intern Med* 2009; 151(5): 306–314.
  51. Lean ME, Leslie WS, Barnes AC et al. Primary care-led weight management for remission of type 2 diabetes (DIRECT): An open-label, cluster-randomised trial. *Lancet (London)* 2018; 391(10120): 541–551.
  52. Wing RR, Lang W, Wadden TA et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care* 2011; 34(7): 1481–1486.
  53. Yumuk V, Tsigos C, Fried M et al. European guidelines for obesity management in adults. *Obes Facts* 2015; 8(6): 402–424.
  54. Pharr JR, Coughenour CA, Bungum TJ. An assessment of the relationship of physical activity, obesity, and chronic diseases/conditions between active/obese and sedentary/normal weight American women in a national sample. *Public Health* 2018; 156: 117–123.
  55. Antza C, Stabouli S, Natsis M et al. Obesity-induced hypertension: New insights. *Curr Pharm Des* 2017; 23(31): 4620–4625.
  56. Mancia G, Cannon CP, Tikkanen I et al. Impact of Empagliflozin on blood pressure in patients with type 2 diabetes Mellitus and hypertension by background antihypertensive medication. *Hypertension* 2016; 68(6): 1355–1364.
  57. Neal B, Perkovic V, Mahaffey KW et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377(7): 644–657.
  58. Ott C, Jumar A, Striepe K et al. A randomised study of the impact of the SGLT2 inhibitor dapagliflozin on microvascular and macrovascular circulation. *Cardiovasc Diabetol* 2017; 16(1): 26.

59. Wanner C, Inzucchi SE, Lachin JM et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016; 375(4): 323–34.
60. Marso SP, Daniels GH, Brown-Frandsen K et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; 375(4): 311–322.
61. Frias JP, Guja C, Hardy E et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): A 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol* 2016; 4(12): 1004–1016.
62. Sjostrom L, Lindroos AK, Peltonen M et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004; 351(26): 2683–2693.
63. Sjostrom L. Review of the key results from the Swedish Obese Subjects (SOS) trial: A prospective controlled intervention study of bariatric surgery. *J Intern Med* 2013; 273(3): 219–234.
64. Sjolholm K, Pajunen P, Jacobson P et al. Incidence and remission of type 2 diabetes in relation to degree of obesity at baseline and 2 year weight change: The Swedish Obese Subjects (SOS) study. *Diabetologia* 2015; 58(7): 1448–1453.



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# HYPERTENSION IN CHILDREN AND ADOLESCENTS

# 52

*Empar Lurbe and Pau Redon*

## INTRODUCTION

The available data concerning childhood blood pressure (BP) has increased substantially over the last four decades. Clinicians can use the available paediatric reference BP data to determine whether BP is in the normal range or is at a level that warrants evaluation or preventive intervention. Findings that are becoming ready to incorporate into clinical use include data showing the importance of detecting high-normal BP, the meaning of BP obtained out of the clinic setting and the importance of central BP determinations, clinical significance of isolated systolic hypertension (ISH), new risk factors for hypertension (HTN), clustering of cardiovascular (CV) risk factors, and treatment strategies, among others.

## DEFINITION AND DIAGNOSIS OF HYPERTENSION

Unlike for adults, the definition of HTN in children is arbitrary and is based on the normal distribution of BP in healthy children and not on the CV morbidity and mortality associated with a certain level of BP. Diagnostic criteria for elevated BP in children are based on the concept that BP in children increases with age and body size, making it impossible to utilize a single BP level to define HTN, as is done in adults. Because of the persisting lack of European reference values that incorporate age, sex and height throughout the entire paediatric age range, the normative data on auscultatory clinical measurements provided by the US Task Force (1) are recommended to use as reference values (2,3), although the potential differences among countries and ethnicities should be considered.

In 2009 the ESH Guidelines in children and adolescents were released (2). The criteria to define BP categories were: normal BP defined as systolic BP (SBP) and diastolic BP (DBP) less than 90th percentile for age, sex and height; HTN defined as SBP and/or DBP persistently 95th percentile or more, measured on at least three separate occasions with the auscultatory method. Children with average SBP or DBP 90th percentile or more but less than 95th percentile classified as having high-normal BP.

The 2016 Guidelines (3) introduced a new criteria for boys and girls 16 or older, since considering the 95th percentile for age, sex and height as the definition of HTN, a 16-year-old boy in the 95th percentile for height would be defined as hypertensive by an office SBP of 137–140 mmHg, while a 16-year-old girl in the same height percentile would be defined as hypertensive by an office SBP of only 132 mmHg. One to two years later, no longer seen by a paediatrician, the girl will now be diagnosed as normotensive or high-normal by the family physician on the basis of adult guidelines. Even greater differences in diagnosis will occur in adolescents shorter than the 95th height percentile. Due to these differences in diagnosis, a consensus in the 2016 Guidelines is given that for boys and girls aged 16 or older, the definition of HTN should no longer be based on the 95th percentile but on the absolute cutoff used for adults, which defines high-normal (130–139/85–89 mmHg) and HTN ( $\geq 140/90$  mmHg) (3).

The classification and diagnosis of HTN in children and adolescents following the criteria of ESH Guidelines 2016 (3) is shown in Table 52.1.

## PREVALENCE AND INCIDENCE

The prevalence in school-aged children appears to be increasing, perhaps as a result of the increased prevalence of obesity in the last years. The majority of these children have mild HTN, most often primary. A small group of children have much higher BPs, usually due to a secondary cause.

The prevalence of HTN in children and adolescents in Europe is reported to be ranging from 2.2–22% (4–9) depending on the demographic characteristics of the subjects analysed, age, sex and body weight as well as ethnicity. More specifically, HTN increases with age, and in boys rather than in girls. Body weight has the greatest impact on the rate of HTN, and the body mass index is the strongest determining factor of adolescent BP (5). One study has reported a 27 and 47% in overweight or obese 6- to 18-year-old subjects (9). A higher BP in Hispanics and African Americans and a lower one in Asians, when either is compared to Caucasians, were observed (10).

Besides the characteristics of the subjects, the number of BP measurements is crucial in the prevalence of HTN.



**Table 52.1** Classification of hypertension in children and adolescents

|                                | 0–15 years                                         | 16 years and older    |
|--------------------------------|----------------------------------------------------|-----------------------|
| Category                       | SBP and/or DBP Percentile                          | SBP and/or DBP values |
| Normal                         | <90th                                              | <130/85 mmHg          |
| High-normal                    | ≥90th to <95th percentile                          | 130–139/85–89 mmHg    |
| Hypertension                   | ≥95th percentile                                   | ≥140/90 mmHg          |
| Stage 1 Hypertension           | 95th percentile to the 99th percentile plus 5 mmHg | 140–159/90–99 mmHg    |
| Stage 2 Hypertension           | >99th percentile plus 5 mmHg                       | 160–179/100–109 mmHg  |
| Isolated systolic hypertension | SBP ≥95th percentile and DBP <90th percentile      | ≥140/<90 mmHg         |

Source: Lurbe E et al. *J Hypertens* 2016; 34(10):1887–1920.

Statistically, 5% of children had a BP measurement above the 95th percentile during a single office visit; however, BP tended to normalize on subsequent measurements due to the accommodation of the child to the measurement procedure and to the statistical phenomenon of regression towards the mean (11). Consequently, the prevalence of HTN decreased after repeated examination.

Clinically relevant are the studies in incidence that addressed the concern with progression from high-normal BP to HTN. Some groups of children with masked HTN, type 2 diabetes mellitus, obesity or repaired aortic coarctation have an increased risk to progress. In contrast, in the general population of adolescents, 10–19 years, the rate of progression from normotension to HTN was 0.4/100 subjects/year, and among those who had high-normal it was 1.1/100 subjects/year (12). In normotensive children the risk is higher in boys than in girls (13).

### IN- AND OUT-OFFICE BLOOD PRESSURE: WHITE-COAT AND MASKED HYPERTENSION

Blood pressure variability and observer bias limit the reliability of office measurements that have the potential for inaccuracies (14). Automated techniques of BP out-of-office measurement may overcome these limitations; therefore ambulatory BP monitoring, and also home BP measurements, became an established instrument for the diagnosis and follow-up of HTN in children and adolescents (15). Recommendations for the use of ambulatory BP and home BP measurements are presented in the recent 2016 Guidelines (3). The recommendations for 24-hour ambulatory BP monitoring were during the process of diagnosis, during antihypertensive treatment, clinical trials and

other clinical conditions like autonomic dysfunction and suspicion of catecholamine-secreting tumours.

Office and ambulatory BP do not necessarily agree. So-called white-coat HTN and masked HTN are conditions in which BP is discrepant from the majority of a person's BPs, depending on the setting. White-coat HTN is defined as elevated BP in an office setting, yet normal BP elsewhere. The reported frequency of white-coat HTN varies, perhaps as a result of the criteria used to establish the diagnosis, with values ranging from very low (1%) to as high as 44% (16). Children with white-coat HTN tend to have an intermediate left ventricular mass (LVM) index between that of normotensive patients and patients with sustained HTN, suggesting that white-coat HTN may be associated with hypertensive end-organ damage (17).

The inverse phenomenon, masked HTN, defined as normal BP in the office setting but elevated BP outside the office occurs in approximately 10% of children and adolescents (18–20). The persistence and clinical significance of the phenomenon was analysed in a prospective study involving 234 adolescents (20). In 40%, the abnormal elevation of the daytime ambulatory BP persisted over a minimum of 6 months. Adolescents with persistent masked HTN were more than twice as likely as those without it to have a parental history of HTN, higher ambulatory pulse rate, higher body mass index and more frequently had left ventricular hypertrophy (LVH) than did normotensive subjects. Alone or in combination, these findings were associated with a predisposition to the development of persistent HTN and were linked to increased cardiovascular risk in later life (20).

### CENTRAL BLOOD PRESSURE AND THE CASE OF ISOLATED SYSTOLIC HYPERTENSION

Central BP values in the aortic root may be estimated by calculations from the pulse wave recorded in peripheral arteries, either radial or carotid. Central BP values are usually lower than those obtained from the brachial artery. The differences between central and peripheral values, the so-called amplification phenomenon, depends on the elastic properties of the aorta and the large vessels, as well as the distance between the peripheral point of recording and the aortic root – the greater the distance, the greater the difference. Elasticity of the great vessels is particularly relevant in adolescence and causes systolic BP to be considerably higher in upper limb arteries than in the ascending aorta and left ventricle. This phenomenon results in isolated systolic HTN, the main HTN subtype in youth.

Isolated systolic HTN in young people, defined on the basis of brachial BP as a SBP of at least 140 mmHg with a diastolic BP of <90 mmHg, is not an unusual condition and is increasing in prevalence. To date, this concept has been confronted with challenges in the mechanisms, clinical relevance and consequences. Parameters other than brachial BP, such as noninvasive central hemodynamics, have introduced new insights to the condition. Nevertheless, grounded information supporting the long-term consequences is still lacking; therefore, the necessity to decide to treat or not to treat is a matter of concern in clinical practice (21).

## AETIOLOGY

Paediatric HTN is associated with a broad spectrum of diseases that changes from childhood through adolescence. Definable causes of HTN are the rule in the early years of life, whereas essential HTN is more common in adolescence. Consequently, techniques for the evaluation and diagnosis of HTN differ, at least in part, among the different age groups.

Usually, sustained HTN in children and adolescents is classified as secondary with a specific cause that may be correctable or as essential and without an identifiable cause (2). The most common causes of HTN can change during childhood. Essential HTN is rarely seen in infants and young children, but its prevalence increases significantly in adolescence. A good general rule to follow is that the likelihood of identifying a secondary cause of HTN is inversely related to the age of the child and directly related to the degree of BP elevation. Consequently, the evaluation of children with HTN, especially young children and those with severe HTN, should be comprehensive and aimed at identifying known causes of the disease.

The distribution of definable causes of HTN is associated with a broad spectrum of diseases and clearly varies with age. Renal parenchymal disorders predominate, accounting for a majority of secondary causes (22). Renal parenchymal disorders with renovascular disease and coarctation of the aorta account for 70 (23) to 90% (24) of all cases. These figures vary depending not only on the age group, but also on referral centre and referral bias. In addition, HTN is often related to prescribed drugs with hypertensive potential. Other infrequent causes of sustained HTN, tumours and central nervous and endocrine disorders, must be considered once more common causes of secondary HTN have been eliminated. An emerging cause of secondary HTN is a single-gene mutation that produces large changes in BP (3).

In very young children (<6 years), HTN is most often the result of such renal parenchymal disease as glomerulonephritis, renal scarring, polycystic kidney diseases and renal dysplasia. Renal artery stenosis and cardiovascular disorders like coarctation of the aorta, less frequent causes of HTN in this age group, are usually detected within the first decade of life. Late in the first decade and throughout the second, essential HTN is the most common cause of sustained HTN, particularly in those children with mild asymptomatic disease (3).

A diagnostic evaluation is based to some degree on the level of BP, age, sex, clinical findings and family history. A significant number of children with secondary forms of HTN, often renal ones, can be identified using a selective approach. Afterwards, a careful selection of the necessary test often shortens the diagnostic process.

## ASSESSMENT OF TARGET-ORGAN DAMAGE

Because overt morbid cardiovascular events are rare in the majority of hypertensive children, attention has focused on other markers of HTN injury, such as early renal damage, increased LVM index (LVMI) and functional or organic vascular abnormalities. Cardiovascular damage develops in parallel to renal damage, although the cardiovascular

sequelae of childhood-onset HTN, such as LVH and dysfunction, and atherosclerosis, may not become clinically relevant before adulthood. More recently, the study of early alterations of central nervous system functions has become a focus of interest.

The abnormal increase of LVM and/or geometry has been recognized as one of the most important markers of risk for HTN-induced cardiovascular morbidity and mortality in adults. In children and adolescents, LVM is normalized for height in metres raised to the allometric power of 2.7, in order to linearize the relation between LV and height. The resulting LVMI is expressed in  $\text{g}/\text{m}^{2.7}$ . More recently reported definitions of LVH are suggested to improve the ability to identify abnormalities in left ventricular geometry; these account for the inverse dependence of the LVMI with body size in infants and young children by using age- and sex-specific partition values for LVH (25).

Cross-sectional studies have indeed shown that the major determinants of left ventricular growth are body size and sex, with a smaller contribution made by BP (26–28). The potential role of adiposity in the increment of LVM has been highlighted. Adiposity and LVM are related in childhood, and this association tracks and becomes stronger in young adulthood.

Studies of normal and hypertensive children have found that systolic BP and LVMI are positively associated across a wide range of BP values, with no clear threshold to predict a pathologically increased LVMI. The relationship between LVMI and systolic BP is more evident when BP is measured using 24-hour ambulatory BP monitoring.

Operational thresholds for LVM have been established. Both the allometric definition of excessive mass ( $>51 \text{ g}/\text{m}^2$ ) as well as the percentile distribution of mass and geometry have been recommended (25). Using these operational thresholds, a few studies have analysed the prevalence of LVH in not only healthy, but also hypertensive children and adolescents. In hypertensive children, the prevalence of LVH ranges from 24–40% in different paediatric studies (29–31). In children with chronic kidney disease, LVH develops relatively early and becomes more prevalent as kidney function decreases (32).

Cardiac end-organ damage from HTN exists in children, and LVM assessment seems to be important in the management of childhood HTN, since it is the most prominent evidence of target-organ damage in childhood HTN. The ESH Guidelines for BP in Children have recommended performing echocardiography in all hypertensive children (2,3). The presence of LVH is an indication to initiate or intensify antihypertensive therapy. Studies assessing the effect of medical therapy of paediatric HTN on LVM need to be performed in the future to further reinforce the necessity of monitoring LVM.

Increased urinary albumin excretion (UAE) is considered a sensitive marker of HTN-induced renal damage. Proteinuria indicates glomerular damage in primary and secondary glomerulopathies and since proteinuria tends to increase with the duration and severity of HTN, it should be targeted by lowering BP. Even small amounts of UAE, microalbuminuria, are correlated with the progression of nephropathy and linked to a higher cardiovascular risk. Initial information came from cross-sectional studies which demonstrated a clustering of cardiovascular risk factors and organ damage associated with even a subtle increase in UAE. The role of microalbuminuria in paediatrics, however, is limited to diabetic children and

adolescents. The prevalence of elevated UAE is not prominent in obese children (2.4%) and when it is increased, it depends mainly on metabolic factors (33). While the significance of microalbuminuria in paediatric essential HTN has yet to be established, routine urinary albumin assessment is recommended by the ESH Guidelines (2,3).

Hypertension-induced abnormalities in arterial structure and function are important because they underlie many adverse effects. Assessment of vascular damage, however, received little attention prior to the advent of the advanced ultrasound technology which permits noninvasive study of vascular walls and lumen. Intima-media thickness measurement at the carotid artery is the most common of the methods to assess structural abnormalities. Since intima-media thickness is influenced by age and sex during childhood and adolescence (34), measured values should be related to percentiles or expressed as standard deviation scores.

Ultrasound examination of the carotid arteries with measurement of intima media thickness and/or the presence of plaques has been shown to predict the occurrence of both stroke and myocardial infarction, independently of traditional CV risk factors (35). In the few paediatric studies available, intima-media thickness tends to be increased in hypertensive children and adolescents compared to normotensive controls (36,37), although one study did not observe differences among normotensives, white-coat, masked or sustained hypertensives (19). Moreover, a relationship between intima-media thickness and endothelial function has been established in the Cardiovascular Risk in Young Finns Study (38). The impact of other cardiovascular risk factors besides HTN, such as cholesterol levels or smoking, needs to be considered in the interpretation of intima-media thickness levels, since these have been associated with intima-media thickness as well (39). The International Childhood Cardiovascular Cohort Consortium demonstrated that individuals with persistently elevated BP from childhood to adulthood had increased risk of carotid atherosclerosis. This risk was reduced if elevated BP during childhood resolved by adult age (40). Moreover, measurement is not trivial and is subject to some observer bias. Hence, despite the increasing evidence for its predictive value in cardiovascular disease, carotid intima-media thickness assessments have not yet been recommended universally for routine clinical use (2,3).

Traditional diagnostic procedures to assess early organ damage in the central nervous system included neurologic and ophthalmologic clinical evaluation, electroencephalography and, in emergency cases, cranial magnetic resonance image to exclude intracranial haemorrhage or cerebral oedema. Magnetic resonance imaging has largely replaced the computerized tomography scan, due to its better detection of small silent brain infarcts, microbleeds and white matter lesions (2,3).

As paediatric HTN is on the rise, there has been increased interest in evaluating its impact on neurocognitive function. There is now emerging evidence that children with HTN manifest neurocognitive differences when compared with normotensive controls, potentially representing early signs of hypertensive target-organ damage to the brain. Preliminary evidence suggests that children with HTN may manifest deficits on measures of neurocognition. They have an increased prevalence of learning difficulties and have altered cerebrovascular reactivity. Children with HTN associated with obesity may be at

increased risk for depression and anxiety in comparison to their normotensive and/or non-overweight peers (41). Neurocognitive studies of children have focused principally on cognitive domains of attention and working memory, executive functions and recall of newly learned information. However, paediatric reports to date have been limited to database and single-centre studies (42). The practical implications of the potential neurocognitive deficits associated with HTN in childhood are not clear. It is even less clear whether there would be any implications for longer-term cognitive reserve and ultimate cognitive decline in later life (43,44). Meanwhile, clinicians should be aware of these emerging concerns. Arterial HTN should be ruled out routinely in children with deteriorating cognitive function, and referral for neurocognitive testing should be considered in children with HTN who are struggling academically.

## WHEN TO INITIATE ANTIHYPERTENSIVE TREATMENT

Currently the initial treatment for children and adolescents with less severe HTN and those with primary HTN and no hypertensive target-organ damage involves lifestyle modifications: weight reduction, exercise and dietary intervention (3). Weight reduction has been shown to be an effective therapy for obese children with HTN. Weight reduction in children is a goal that is difficult to achieve in the long run. Exercise helps to reduce systolic and diastolic BP levels as well as it does weight. Diets with a high intake of fruits, vegetables, low-fat dairy and whole grains while reducing the intake of foods high in saturated fat and refined sugar are recommended. Dietary salt restriction has a very important place in the control of BP. The current recommendation for adequate daily sodium intake is only 1.2 g/day for 4- to 8-year-olds and 1.5 g/day for children older than that.

Although conservative measures clearly can reduce BP, these options are often insufficient for achieving the treatment goal. The decision to initiate pharmacologic treatment in the first or second decade in the absence of symptoms and in otherwise healthy individuals is not easy, since the long-term consequences of untreated HTN and the benefits of therapy remain unknown. For these reasons, a definitive indication for initiating pharmacologic treatment should be ascertained before medication is prescribed in a child or adolescent. The indications for antihypertensive therapy are symptomatic HTN, secondary HTN, hypertensive target-organ damage, diabetes and persistent HTN despite non-pharmacologic measures (3).

## HOW TO INTRODUCE ANTIHYPERTENSIVE PHARMACOLOGICAL TREATMENT, AND GOALS TO ACHIEVE

In making pharmacological treatment decisions for children, clinicians previously had to adapt the results of adult trials in selecting antihypertensive agents. This approach, although possibly effective in lowering BP, is fraught with problems, especially the unknown differences in both the metabolism and adverse effect profiles of these drugs in



children versus adults, as well as the unknown long-term effects of antihypertensive medications on the growth and development of children. Off-label use, with all of its implied risks, has often been the only option available to physicians who treated children with HTN.

No particular class of antihypertensive drugs has been shown to be superior to another in terms of its effect in children. In some cases, the choice of antihypertensive agent depends on the underlying cause. When choosing among the available therapies, the clinician must also consider efficacy, dosing availability and frequency, adverse effects and cost. Taking into account that compliance is a very important issue, if BP control can be achieved with a single drug that is taken once a day, it will improve compliance and should be taken into consideration when the initial agent is chosen. If monotherapy is introduced, and after titration BP control is not achieved, the next step is to add a second drug. The choice of the drug to be added needs to look for additive antihypertensive activity and to buffer potential secondary effects. Therapy must be monitored closely both for efficacy and potential adverse effects. Efficacy in reducing BP values should be monitored by using both office and out-of-office BP measurements.

The goal of treatment for HTN is to decrease the short- and long-term risks of cardiovascular, neurological and renal disease. Reducing BP alone is insufficient to obtain this objective; the issues of obesity, hyperlipidaemia, smoking and glucose intolerance must also be addressed if present.

The target BP goal in children with uncomplicated primary HTN and no hypertensive target-organ damage should be <95th percentile for gender, age and height but it is probably wiser and safer to aim at a BP below the 90th percentile, provided this goal can be attained by well-tolerated treatment. For children with chronic renal disease, diabetes or hypertensive target-organ damage, the goal BP should be <75th percentile (3). Evidence for this was established in the prospective randomized ESCAPE Trial, which showed better 5-year renal survival in children with chronic kidney disease when strict BP control below the 50th percentile of mean arterial pressure was aimed for (45).

After starting treatment, the frequency of office BP readings depends on the severity of HTN and on the given BP goal. Stage 2 HTN or stage 1 in the presence of cardiac or renal failure needs to be monitored weekly until the goal is achieved. In subjects with diabetes or organ damage, a monthly check may be appropriate. At-home BP monitoring can help in long-term control and even improve compliance. Twenty-four-hour ambulatory BP monitoring is recommended in cases of resistant HTN, progression of organ damage despite apparent good BP control and in those with frequent circadian variability abnormalities, chronic renal failure and diabetes mellitus. Female patients of childbearing potential should be counselled about the need to use an effective method of contraception when treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker is indicated, because exposure to these drugs, especially in the first trimester, may have adverse effects on the developing fetus (46).

The success of a given antihypertensive treatment, however, is difficult to estimate solely by the extent of BP reduction, in part due to the impact of BP values on risk, which depends on the existence of underlying organ damage and the coincident influence of other cardiovascular

risk factors. Then, above and beyond BP values in an individual subject, it is necessary to monitor the impact of antihypertensive treatment in the development or regression of HTN-induced early end-organ damage. Among the potential intermediate endpoints, LVH seems to be the most useful in this age group. Assessment and monitoring of these intermediate objectives may play an important role in providing scientific evidence for delineating the best antihypertensive treatment to apply. Although improvement in the intermediate endpoints may be followed by a substantial reduction of risk, the potential differences in success among the different classes of drugs is still a matter of debate.

In some patients, in whom treatment is accompanied by effective BP control for an extended period, it may be possible to reduce the number and dose of drugs. This may particularly be the case if BP control is accompanied by healthy lifestyle changes, such as weight loss, exercise habits and a low-fat and low-salt diet, which remove environmental pressor influences. Reduction of medications should be made gradually, and the patient should frequently be checked because of the risk of reappearance of HTN.

## FUTURE PATHS

Several unmet knowledge gaps about BP and its consequences in children and adolescents remain. A growing body of evidence supports the concept that high-normal BP is not benign and is likely to be associated with the presence of early target-organ damage. This raises the question of whether the 95th percentile criteria for HTN capture current and subsequent cardiovascular disease risk and if it is possible to detect early biomarkers that herald the progression to higher BP values.

Besides BP values, better knowledge about the natural history of early organ damage is necessary. The assessment of organ damage needs to be optimized, looking for early markers, not only for diagnosis but also for assessing changes during treatment.

Perinatal programming opens up new ways to understand the early-life origins of diseases such as HTN and diabetes, but also introduces relevant challenges in understanding the potential mechanisms involved. Making careful phenotypic observations and pairing them with molecular markers will need to be integrated into prospective studies. Newer tools of molecular medicine are increasingly available and have the potential to deepen our understanding of these intriguing associations.

Developing insights into the interactions among clustering cardiometabolic risk factors in target-organ injury will contribute to a more accurate estimation of the underlying cardiovascular pathology among adolescents with elevated BP. Understanding the interactions among all of these factors in the development of target-organ damage is critical.

In children and adolescents, pivotal information remains unanswered, and therefore a plan of action needs to be developed, looking for a definition of HTN, appropriate goals, and ambulatory BP-guided therapy to obtain greater reductions in organ damage compared to office BP. Better knowledge of all of these may contribute to optimizing interventions, reducing organ damage and improving long-term prognosis.

## REFERENCES

- National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004; 114: 555–576.
- Lurbe E, Cifkova R, Cruickshank JK et al. A Management of high blood pressure in children and adolescents: Recommendations of the European Society of Hypertension. *European Society of Hypertension. J Hypertens* 2009; 27: 1719–1742.
- Lurbe E, Cruickshank JK, Dominiczak A et al. European Society of Hypertension (ESH) Guidelines for the management of high blood pressure in children and adolescents. *J Hypertens* 2016; 34(10): 1887–1920.
- Chiolero A, Cachat F, Burnier M et al. Prevalence of hypertension in schoolchildren based on repeated measurements and association with overweight. *J Hypertens* 2007; 25: 2209–2217.
- Katona É, Zrínyi M, Lengyel S et al. The prevalence of adolescent hypertension in Hungary - the Debrecen hypertension study. *Blood Press* 2011; 20: 134–139.
- Ostrowska-Nawarycz L, Nawarycz T. Prevalence of excessive body weight and high blood pressure in children and adolescents in the city of Łódź. *Kardiol Pol* 2007; 65: 1079–1087.
- Akgun C, Dogan M, Akbayram S et al. The incidence of asymptomatic hypertension in school children. *J Nippon Med Sch* 2010; 77: 160–165.
- Maldonado J, Pereira T, Fernandes R et al. An approach of hypertension prevalence in a sample of 5381 Portuguese children and adolescents. The AVELEIRA registry. 'Hypertension in children'. *Blood Press* 2011; 20: 153–157.
- Flechtner-Mors M, Neuhauser H, Reinehr T et al. APV initiative and the BMBF Competence Network Obesity. Blood pressure in 57,915 pediatric patients who are overweight or obese based on five reference systems. *Am J Cardiol* 2015; 115: 1587–1594.
- Harshfield GA, Wilson ME. Ethnic differences in childhood blood pressure. In: Portman RJ, Sorof JM, Ingelfinger JR (eds). *Pediatric Hypertension*. Humana Press, Totowa, NJ; 2004: 293–305.
- Gardner LS, Haddy JA. Some effects of within-person variability in epidemiological studies. *J Chronic Dis* 1973; 26: 781–795.
- Redwine KM, Acosta AA, Poffenbarger T et al. Development of hypertension in adolescents with Pre-hypertension. *J Pediatr* 2012; 160: 98–103.
- Lurbe E, Thijs L, Torro MI et al. Sexual dimorphism in the transition from masked to sustained hypertension in healthy youths. *Hypertension* 2013; 62: 410–414.
- O'Brien E, Asmar R, Beilin L et al. European Society of Hypertension Working Group on blood pressure monitoring. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003; 21: 821–848.
- Ingelfinger JR. The child or adolescent with elevated blood pressure. *N Engl J Med* 2014; 370: 2316–2325.
- Lurbe E, Torro MI, Alvarez J. Ambulatory blood pressure monitoring in children and adolescents: Coming of age? *Curr Hypertens Rep* 2013; 15: 143–149.
- Kavey RE, Kveselis DA et al. White coat hypertension in childhood: Evidence for end-organ effect. *J Pediatr* 2007; 150: 491–497.
- Matsuoka S, Awazu M. Masked hypertension in children and young adults. *Pediatr Nephrol* 2004; 19: 651–654.
- Stabouli S, Kotsis V, Tzoumanidis S et al. White-coat and masked hypertension in children: association with target organ damage. *Pediatr Nephrol* 2005; 20: 1151–1155.
- Lurbe E, Torro I, Alvarez V et al. Prevalence, persistence, and clinical significance of masked hypertension in youth. *Hypertension* 2005; 45: 493–498.
- Lurbe E, Redon J. Isolated systolic hypertension in young people is not spurious and should be treated: Con side of the argument. *Hypertension* 2016; 68: 276–280.
- Goonasekera CDA, Dillon MJ. Measurement and interpretation of blood pressure. *Arch Dis Child* 2000; 82: 261–265.
- Arar MY, Hogg RJ, Arant BS, Seikaly MG. Etiology of sustained hypertension in children in the Southwestern United States. *Pediatr Nephrol* 1994; 8: 186–189.
- Lieberman E. Hypertension in childhood and adolescence. In: Kaplan N (ed). *Clinical Hypertension*. 5th ed. Williams and Wilkins, Baltimore, MD; 1990: 407–433.
- Khouri PR, Mitsnefes M, Daniels SR, Kimball TR. Age-specific reference intervals for indexed left ventricular mass in children. *J Am Soc Echocardiogr* 2009; 22: 709–714.
- Malcolm DD, Burns TL, Mahoney LT, Lauer RM. Factors affecting left ventricular mass in childhood: The Muscatine Study. *Pediatrics* 1993; 92: 703–709.
- de Simone G, Devereux RB, Daniels SR et al. Effect of growth on variability of left ventricular mass: Assessment of allometric signals in adults and children and their capacity to predict cardiovascular risk. *J Am Coll Cardiol* 1995; 25: 1056–1062.
- Foster BJ, Gao T, Mackie AS et al. Limitations of expressing left ventricular mass relative to height and to body surface area in children. *J Am Soc Echocardiogr* 2013; 26: 410–418.
- Sivanandam S, Sinaiko AR, Jr JD et al. Relation of increase in adiposity to increase in left ventricular mass from childhood to young adulthood. *Am J Cardiol* 2006; 98: 411–415.
- Litwin M, Niemirska A, Sladowska J et al. Left ventricular hypertrophy and arterial wall thickening in children with essential hypertension. *Pediatr Nephrol* 2006; 21: 811–819.
- Daniels SR, Loggie JM, Khouri P, Kimball TR. Left ventricular geometry and severe left ventricular hypertrophy in children and adolescents with essential hypertension. *Circulation* 1998; 97: 1907–1911.
- Kavey RE. Left ventricular hypertrophy in hypertensive children and adolescents: Predictors and prevalence. *Curr Hypertens Rep* 2013; 15: 453–457.
- Lurbe E, Torro MI, Alvarez MI et al. Prevalence and factors related to urinary albumin excretion in obese youths. *J Hypertens* 2013; 31: 2230–2236.
- C1 J, Wühl E, Litwin M et al. Normative values for intima-media thickness and distensibility of large arteries in healthy adolescents. *J Hypertens* 2005; 23: 1707–1715.
- Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1281–1357.
- Sass C, Herbeth B, Chapet O et al. Intima-media thickness and diameter of carotid and femoral arteries in children, adolescents and adults from the Stanislas cohort: Effect of age, sex, anthropometry and blood pressure. *J Hypertens* 1998; 16: 1593–1602.
- Sorof JM, Alexandrov AV, Cardwell G, Portman RJ. Carotid artery intimal-medial thickness and left ventricular hypertrophy in children with elevated blood pressure. *Pediatrics* 2003; 111: 61–66.
- Juonala M, Viikari JSA, Laitinen T et al. Interrelations between brachial endothelial function and carotid intima-media thickness in young adults. The cardiovascular risk in young Finns study. *Circulation* 2004; 110: 2918–2923.
- Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. *Circulation* 2001; 104: 2815–2819.
- Juhola J, Magnussen CG, Berenson GS et al. Combined effects of child and adult elevated blood pressure on subclinical atherosclerosis: The International Childhood Cardiovascular Cohort Consortium. *Circulation* 2013; 128: 217–224.
- Lande MB, Kupferman JC, Adams HR. Neurocognitive alterations in hypertensive children and adolescents. *J Clin Hypertens (Greenwich)* 2012; 14: 353–359.
- Lande MB, Adams HR, Kupferman JC et al. A multicenter study of neurocognition in children with hypertension: methods, challenges, and solutions. *J Am Soc Hypertens* 2013; 7: 353–362.
- Kupferman JC, Lande MB, Adams HR, Pavlakakis SG. Primary hypertension and neurocognitive and executive functioning in school-age children. *Pediatr Nephrol* 2013; 28: 401–408.
- Marc Y, Gao J, Balavoine F et al. Central antihypertensive effects of orally active aminopeptidase A inhibitors in spontaneously hypertensive rats. *Hypertension* 2012; 60: 411–418.
- Trial Group ESCAPE, Wühl E, Trivelli A et al. Strict blood-pressure control and progression of renal failure in children. *N Engl J Med* 2009; 361: 1639–1650.
- Cooper WO, Hernandez-Diaz S, Arbogast PG et al. Major congenital malformations after first-trimester exposure to ACE-inhibitors. *N Engl J Med* 2006; 354: 2443–2451.



# HYPERTENSIVE EMERGENCIES AND URGENCIES

# 53

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## INTRODUCTION

Clinicians frequently have to manage acute BP reduction for a critically ill patient, without specific indications established by clinical trials (1–3); antihypertensive drugs are often administered based on pathophysiological considerations and/or according to individual clinical experience. A large number of patients admitted to the emergency department (ED) have longstanding hypertension and should be referred to outpatient care rather than receive acute interventions (4,5).

The mechanisms leading to the acute elevation of BP in patients with hypertensive emergencies remain poorly understood (6). Vascular damage consequent to increased mechanical stress develops rapidly, and vasoconstriction and thrombosis are responsible for ischaemia and disruption of arterial autoregulation (7). Markers of inflammation, coagulation, platelet activation and fibrinolysis are increased in patients with hypertensive emergencies (8), while in patients with malignant hypertension, circulating endothelial progenitor cells are increased (9).

The short-term and long-term effects of acute BP lowering on cardiac and cerebrovascular morbidity and mortality have been evaluated in a few randomized clinical trials (1,10–12).

## DEFINITION

Most recent guidelines have suggested differentiating 'hypertensive crisis', i.e. the acute and severe increase in blood pressure (BP) into 'hypertensive emergency' or 'hypertensive urgency' (1–3).

*Hypertensive emergency* is an acute increase in BP associated with new-onset or worsening target-organ damage, potentially life-threatening and requiring hospitalization and rapid BP control (minutes or a few hours) by the use of intravenous antihypertensive drugs. Hypertensive emergencies most frequently present as acute ischaemic and haemorrhagic stroke, hypertensive acute heart failure (H-AHF), hypertensive encephalopathy, myocardial infarction, but also sympathetic crises (cocaine toxicity/pheochromocytoma), acute aortic dissection and

eclampsia. The main objective of the treatment is to stop the worsening of organ damage and avoid long-term complications (6,10,13–16).

*Hypertensive urgency* is a rapid and severe increase in BP, with or without very mild symptoms suggesting acute organ damage; these patients do not need hospitalization, and oral administration of antihypertensive drugs may be used to reduce BP values. Hypertensive urgencies may be misdiagnosed in patients with uncontrolled hypertension, often associated with poor antihypertensive treatment adherence. In the presence of acute anxiety, panic attacks, painful syndromes, venous epistaxis or alcohol withdrawal, an abrupt BP increase may be observed; the treatment of these conditions is associated with a concomitant reduction of BP.

Sometimes a distinction between hypertensive urgencies and emergencies is not possible, since the unrecognized or undertreatment of a hypertensive urgency may evolve into an emergency.

In most hypertensive emergencies and urgencies, systolic BP (SBP) is higher than 180 mmHg and/or diastolic BP (DBP) is greater than 120 mmHg, indicating the need for a pharmacological intervention (1,2), despite the fact that there is not a consensus on the value of SBP and DBP for the definition of hypertensive emergencies or urgencies (17).

BP values >180 mmHg and/or 110 mmHg were the inclusion criteria in the STAT (Studying the Treatment of Acute hyperTension) registry, but in patients with subarachnoid haemorrhage a lower threshold was defined (SBP ≥140 mmHg and/or DBP ≥90 mmHg) (17). H-AHF (2,10) has been acknowledged by the European Society of Cardiology as a distinct form, defined as the rapid onset of pulmonary congestion in the setting of an SBP >140 mmHg, and often >160 mmHg (18).

Unfortunately, the terms hypertensive 'emergency' or 'urgency' do not correspond to ICD system codes, and some definitions used formerly such as malignant and accelerated hypertension are still used for reimbursement. Accelerated hypertension implies SBP >179 mmHg or DBP >109 mmHg associated with ocular haemorrhages, exudates, and/or papilledema which can be associated with encephalopathy and acute deterioration in renal function.

Malignant hypertension originally described severe hypertension with renal failure, retinopathy with papilledema, fibrinoid necrosis, uraemia, and accelerated death, but has been also used to define acute hypertension with presence of bilateral retinal flame shaped haemorrhages and cotton-spot exudates or papilledema; this term has been removed in international BP control guidelines (13). Recently, the use of acute hypertensive microangiopathy has been proposed (7).

## EPIDEMIOLOGY

Hypertensive emergencies occur in up to 2–3% of hypertensive patients (19–21) with a progressive decrease in mortality rate over the past 4 decades. Among hypertensive ‘crises’, the prevalence of hypertensive emergencies and urgencies is about 25 and 75%, respectively.

In patients with both hypertensive emergencies and urgencies, the incidence of cardiovascular (CV) events is still high (20,22,23). In the United States, increasing age, male sex and a higher Charlson Comorbidity Index were among the stronger predictors of mortality for patients hospitalized for a hypertensive emergency (24). In the Studying the Treatment of Acute hypertension (STAT) registry, a 6.9% hospital mortality and 37% 90-day readmission rate were reported in hypertensive emergencies (17); readmission for hypertension was significantly associated with lack of compliance to the antihypertensive treatment, substance abuse and dialysis (25).

Recently, among patients presenting in an office setting with a hypertensive urgency (26), a low percentage (0.7%) were referred to the emergency room. Patients with renal disease, African American race, and higher SBP and DBP were more frequently hospitalized, without a more favourable outcome.

The optimal screening, treatment and follow-up intervals, as related to the short-term and long-term clinical outcomes, need to be addressed in the future (5).

## INITIAL EVALUATION

In all patients with an acute increase in BP, a complete history (with particular attention to pre-existing hypertension and target-organ damage [TOD]) and an accurate physical examination are mandatory (10). BP should be measured according to guidelines; a significant difference in BP between the two arms should raise the suspicion of aortic dissection. Repeated measurements of BP should be taken, since in about 30% of patients a spontaneous reduction in BP is observed after a 20–30 minutes of rest (27).

Alcohol consumption, some food ingestion (liquorice), the use of illicit substances (cocaine) (28) or drugs (in particular corticosteroids and mineralocorticoids, oestrogens, NSAIDs, cyclosporine, carbamazepine, metoclopramide and angiotensin inhibitors) should be investigated. Urine analysis, creatinine, urea, electrolytes and a full blood count, an electrocardiogram and a chest radiogram should be obtained. Further investigations including echocardiography (29,30), brain CT scan, thoracic and abdominal ultrasound or CT scan, and vascular ultrasound should be performed according to the clinical presentation. A fundoscopic examination (17,31) is part of the examination; in addition to traditional ophthalmoscopy, the use of new smartphone devices seems promising in identifying grade 3–4 Keith–Wegener retinopathy (31) (Figure 53.1).



**Figure 53.1** Example of papilledema. Image taken with a smartphone device for fundoscopy.

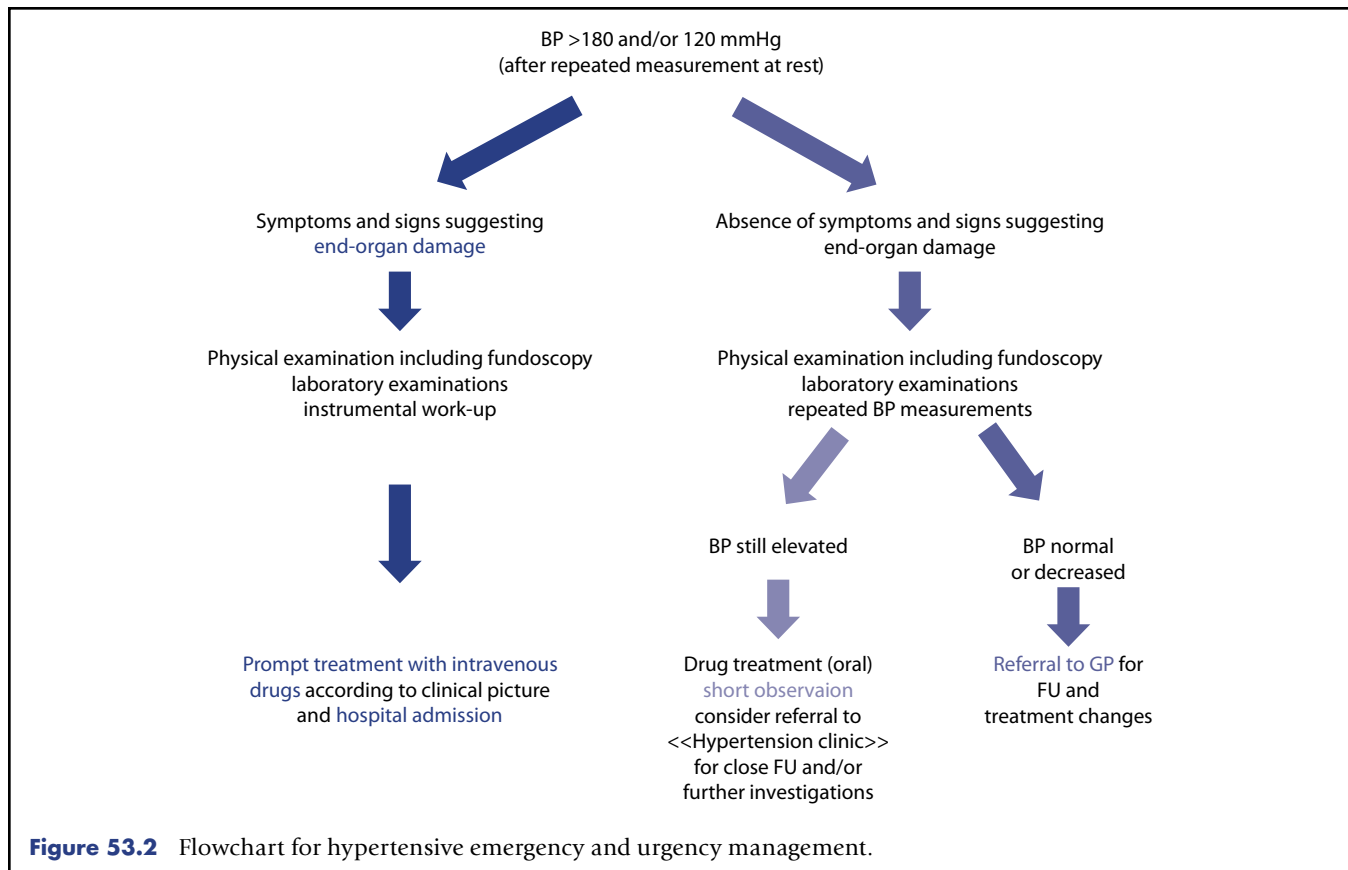
## TREATMENT IN HYPERTENSIVE URGENCY

The best therapeutic approach is the oral administration of antihypertensive drugs, aimed to lower BP gradually over 24–48 hours (1–3,10). A short stay in an observation unit is usually appropriate, without the need of hospital admission; a short-term outpatient visit by a hypertension specialist is strongly suggested (Figure 53.2). A recent study evaluating 58,535 patients with a hypertensive urgency (26) showed that 65% of patients admitted to the ED had uncontrolled hypertension at 6 months follow-up.

The reduction in BP should be gradual, as no benefit, but potential harm, may be associated with a too-rapid BP decrease due to a rightward shift in the pressure/flow autoregulatory curve in critical arterial beds (32,33). The use of a calcium-antagonist or a combination of antihypertensive drugs may favour an effective BP reduction and can be considered for the initial approach, while all guidelines recommend against the use of sublingual administration of nifedipine, as it induces an unpredictable, often too-fast and large decrease in BP (34). In patients with a hypertensive urgency, a similar BP reduction was obtained by treatment with a low dose of telmisartan and by bed rest (35), underlying the efficacy of resting in managing hypertensive urgency, mainly in those with emotional stress or sympathetic overactivity (36).

## TREATMENT IN HYPERTENSIVE EMERGENCY

In hypertensive emergencies, the NHLBI, the 2013 ESH/ESC guidelines (1) and the 2017 multisociety AHA/ACC guidelines (3) suggest a similar approach and recommend reducing mean BP by  $\leq 25\%$  for the first hour, and then to 160/100–110 mmHg by 2–6 hours with subsequent gradual normalization in 24–48 hours. The admission to an ICU for observation and continuous BP monitoring



is recommended. Prompt intravenous administration of short-acting and titratable drugs is the preferred approach (Figure 53.2). The reduction in BP should start in few minutes and progressively increase; a normalization (i.e. <140/90 mmHg) should be gradually achieved in several hours and days (1–3). The only exception to this is aortic dissection, in which the fastest reduction of BP to less than 120/80 mmHg is mandatory (37).

The effect of the rapid-acting intravenous agents available for the treatment of hypertensive emergencies should be carefully monitored in order to avoid an excessive velocity of BP reduction, leading to ischaemic complications such as acute myocardial infarction and stroke, because of altered autoregulation. Unfortunately, the rate of change of BP is frequently greater than recommended (38,39), even in acute stroke patients, in whom the risk of hypoperfusion is well known.

No data are currently available about the different effects among antihypertensive drugs on morbidity and mortality in patients treated for a hypertensive emergency, as underlined by a systematic Cochrane review in which a selected antihypertensive agent was compared with placebo, no treatment, or another drug in a different class (12).

## CHOICE OF TREATMENT

The choice of the best drug(s) with the better benefit–risk ratio depends on the correct recognition of the clinical picture and the consideration of comorbidities.

## ACUTE HEART FAILURE

In patients presenting with dyspnoea and the suspicion of H-AHF, it is crucial to obtain an ECG and an echocardiogram to evaluate diastolic and systolic function and/or mitral or aortic valve regurgitation. Thoracic ultrasound is also indicated to assess the presence of comet tails. BNP or NT-proBNP may be used for new-onset or decompensated AHF diagnosis in the ED and may improve prognosis or risk stratification (40).

Guidelines suggest the use of a loop diuretic and a vasodilator for the aggressive reduction of BP in H-AHF (18,41). Intravenous loop diuretics (furosemide, bumetanide and torasemide) should be administered in all patients (42). Furosemide should be administered as soon as possible (43), since early treatment (time from patient arrival at the ED to the first intravenous furosemide injection <1 hour) with intravenous loop diuretics was associated with lower in-hospital mortality. The DOSE study has shown no differences between bolus every 12 hours or continuous infusion of furosemide (44).

Nitroglycerin, a venodilator, acts as an arteriolar dilator only in high doses. Intravenous administration of nitrovasodilators in the treatment of H-AHF in ED and ED-like settings is associated with an improvement in short-term symptoms, relatively few side effects and no impact on mortality (45).

Other vasodilators, such as hydralazine and enalaprilat, have very little published data about their safety and efficacy (46).

Clevidipine is a third-generation calcium antagonist inhibiting selectively extracellular calcium influx through the L-type channel, relaxing smooth muscle of small arteries and reducing peripheral vascular resistance. The advantages of clevidipine are the blood metabolism, the very short (1-minute) half-life and the rapid titration (42,47) with minimal effects on stroke volume, cardiac output or heart rate. In the PRONTO study (48) clevidipine reduced SBP and improved dyspnoea more effectively than standard treatment did, with a reduction in the need of additional IV antihypertensive drugs and in the total dose of furosemide. In AHF, several other promising drugs including ularitide, an analogue of urodilatin, and serelaxin, a recombinant version of human relaxin-2, are currently under investigation (18).

The use of morphine is controversial, despite the evidence that morphine has vasodilator properties and may reduce preload and the sympathetic drive, and also it decreases dyspnoea.

Noninvasive ventilation may be used to relieve symptoms in patients with pulmonary oedema and severe respiratory distress, or in those patients who fail to improve with pharmacological therapy (41).

## ACUTE STROKE

Hypertension is common in the first hours after ischaemic and haemorrhagic stroke.

## ISCHAEMIC STROKE

Hypertension is a common early finding in patients with an acute ischaemic stroke. The increase in BP usually follows the onset of cerebral ischaemia and is transient (24–48 hours). Impaired neurogenic CV control, autonomic dysregulation, baroreflex failure, increased sympathetic

drive, reflex response to cerebral ischaemia and mental stress may explain the BP rise. However, a high baseline BP should not always be considered deleterious, and the use of antihypertensive drugs for BP reduction is not always advisable in patients with acute ischaemic stroke (49). In the CATIS trial (China Antihypertensive Trial in Acute Ischaemic Stroke), BP reduction with antihypertensive medications did not reduce the likelihood of death and major disability at 14 days or hospital discharge compared with the absence of hypertensive medication (50).

In the early (the first 24–48 hours) phase of ischaemic stroke, a BP fall may be critical, reducing cerebral perfusion, extending the ischaemic area and inducing irreversible damage due to the loss of cerebral flow autoregulation; therefore, during the first 24–48 hours, a high BP may be seen as a compensatory mechanism until the autoregulation is restored. Conversely, in the later phase, a smooth rate of BP reduction is recommended in order to reduce the risk of cerebral oedema, haemorrhagic transformation, stroke recurrence and CV complications. Unfortunately, in acute ischaemic stroke it is very difficult to anticipate the effect of BP changes on cerebral perfusion, even when a thrombolytic agent is administered.

The American Stroke Association (ASA) recommends that only BP values repeatedly above 220/120 mmHg should be treated with intravenous either labetalol or sodium nitroprusside, unless there are other indications for antihypertensive therapy (congestive heart failure, myocardial infarction, aortic dissection) (49).

The BP target during the acute phase of an ischaemic stroke should not be a normal BP, but rather 180 mmHg systolic–105 mmHg diastolic in previously hypertensive patients and 160–180/90–100 mmHg in previously normotensive patients (49); a reasonable goal would be to lower BP by approximately 15% during the first 24 hours after onset of stroke. Different targets are proposed in patients eligible for treatment with intravenous thrombolytics or other acute reperfusion intervention (49) (Table 53.1), while no specific

**Table 53.1** Treatment of ischaemic and haemorrhagic stroke according to baseline and target BP

| Patient                                            | Baseline                  | Target                                              | Drugs                                                               |
|----------------------------------------------------|---------------------------|-----------------------------------------------------|---------------------------------------------------------------------|
| <i>Ischaemic stroke</i>                            |                           |                                                     |                                                                     |
| Previously HT                                      | SBP/DBP >220/120 mmHg     | –15%<br>180/105 mmHg                                | Labetalol or sodium nitroprusside                                   |
| Previously NT                                      | SBP/DBP >220/120 mmHg     | –15%<br>160–180/90/100 mmHg                         | Labetalol or sodium nitroprusside                                   |
| If thrombolytic therapy                            | SBP >185 or DBP >110 mmHg | SBP <180 and DBP <105 mmHg<br>for at least 24 hours |                                                                     |
| Patients not on chronic antihypertensive treatment | SBP/DBP 180–220/<120 mmHg | No treatment for 48 hours                           |                                                                     |
| Patients on chronic antihypertensive treatment     | SBP/DBP >220/120 mmHg     | SBP 180–220 mmHg DBP <120 mmHg                      | Give antihypertensive therapy (labetalol first choice)              |
| <i>Haemorrhagic stroke</i>                         |                           |                                                     |                                                                     |
| Intracerebral haemorrhage                          | SBP 150–220 mmHg          | SBP <140 mmHg                                       |                                                                     |
| Intracerebral haemorrhage                          | SBP >220 mmHg             | Aggressive reduction of BP                          | No indication of a specific drug<br>Continuous intravenous infusion |

Source: Jauch EC et al. *Stroke* 2013; 44: 870–947.



recommendations for target BP are given for patients treated with endovascular therapy.

A systematic meta-analysis of studies evaluating the effect of BP lowering in early ischaemic stroke (51) has included 13 clinical trials, showed no differences in the primary outcome (unfavourable outcome at 3 months or at trial endpoint) and in secondary outcomes, both at short (modified Rankin scale 3–6 and 2–6, all-cause mortality and serious adverse events) and long term (recurrent stroke, recurrent vascular events, modified Rankin score 2–6, all-cause mortality).

A subgroup subanalysis of the CATIS trial (52) has compared the outcome in 4071 acute ischaemic stroke patients with elevated SBP who received antihypertensive treatment or discontinued all antihypertensive medications during hospitalization, and the primary (death and major disability) and secondary outcomes (modified Rankin score, recurrent stroke, vascular disease events, and all-cause mortality) were not significantly different between the treatment and control groups after 2 weeks or at hospital discharge. Death or major disability, recurrent stroke, and vascular events were significantly reduced at the 3-month follow-up in the antihypertensive treatment group only among participants who received treatment between 24 and 48 hours.

Some randomized, controlled studies are currently ongoing, testing the use of transdermal glyceryl-trinitrate (The Rapid Intervention with Glyceryl Trinitrate in Hypertensive Stroke Trial-2, RIGHT-2) (53) given in the ambulance during the first 4 hours after the onset of an acute ischaemic stroke, and the effects of early BP-lowering treatment and compares SBP 130–140 mmHg versus SBP <180 mmHg in patients treated with intravenous alteplase (54).

## HAEMORRHAGIC STROKE

Prevalence of haemorrhagic strokes is 15% of patients. Patients with intracerebral haemorrhage (ICH) often have elevated BP, associated with increased risk of death, disability or neurological deterioration. Increased BP is related to haematoma growth (55) and formation of cerebral oedema. Haematoma expansion is a frequent complication of ICH, occurring in 30% of patients (mainly in the first 24 hours).

Intensive BP lowering in acute ICH is safe and feasible and may be associated with reduced haematoma growth. Rapid BP lowering after a moderate-volume ICH does not alter peri-haematoma cerebral blood flow (56). In the INTERACT-2 (Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial-2) study, intensive lowering of BP did not result in a significant reduction in the rate of the primary outcome of death or severe disability but improved functional outcomes (57). The ATACH-2 (Antihypertensive Treatment in Acute Cerebral Haemorrhage 2) tested the same BP targets in ICH as INTERACT-2, starting treatment at earlier time points (58); the results suggest that intensive SBP reduction is associated with a higher occurrence of serious adverse events within 3 months after randomization, without providing an incremental clinical benefit. Blunting fluctuations in SBP in patients with ICH and an acute hypertensive response may confer a treatment benefit independently of the magnitude of SBP lowering (58,59) (Table 53.1).

The choice of the best drugs for BP reduction in ischaemic or haemorrhagic stroke should be based on a few principles, including rapidity of action, titration and no

fluctuations on cerebral blood flow. In this regard, transdermal agents have inconsistent absorption and efficacy, although stable cerebral perfusion has been observed during glyceryl trinitrate administration (60).

Intravenous labetalol is indicated as a first-line agent for BP control in ischaemic or haemorrhagic stroke, because it has a rapid onset of action and is associated with stable cerebral perfusion.

Urapidil is an alpha-blocker with a central sympatholytic effect mediated via stimulation of serotonin 5HT<sub>1A</sub> receptors in the central nervous system. Intravenous urapidil was suggested to have a potential role in the management of acute stroke, although no studies have specifically investigated the efficacy of urapidil in stroke management. In the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage (INTERACT) study, 47% of patients randomized to intensive BP reduction were treated with urapidil (61).

Intravenous agents such as hydralazine or enalapril have been included as treatment options in stroke guidelines. Hydralazine, however, may be difficult to titrate, with unpredictable effects (62), and may reduce cerebral perfusion through systemic vasodilatation (63). Enalapril was first-line therapy in the CATIS trial, without an increase in adverse events (50).

Nitroprusside is rarely used in acute stroke for BP reduction in the emergency department setting, despite its rapid onset of action, because it needs careful and continuous monitoring and carries a small risk of thiocyanate and cyanide toxicity, although this side effect is seen more commonly with excessive dosing and prolonged use.

Nicardipine has been included in recent guidelines for stroke management (49) and was used in the ATACH-2 study. A systematic review of 10 studies comparing nicardipine and labetalol treatment in hypertensive emergencies has shown comparable efficacy and safety, in spite of more predictable and consistent BP control with nicardipine than with labetalol (64). Nicardipine has been shown to decrease BP more smoothly than sodium nitroprusside or labetalol and to be associated with less BP variability, with stable brain oxygen tension (65–68). Clevidipine could represent an alternative to nicardipine, although it has not been as well studied in stroke as nicardipine.

## ACUTE AORTIC DISSECTION

Arterial hypertension is associated with a higher attributable risk for acute aortic dissection, in addition to more rare genetic syndromes as well as arterial inflammatory diseases (69). In the setting of the ED, the incidence of acute aortic dissection is approximately 1 in 10,000 patients, and only 25% of patients present with the classical pain of sudden onset or ripping/tearing quality, inter-arm BP difference and widened mediastinum on chest radiograph. Type A dissections of the ascending aorta, according to the Stanford classification, are more common, entail a much worse prognosis and may progress proximally, causing hemopericardium with cardiac tamponade, acute aortic valve regurgitation and acute myocardial infarction; Type A and type B dissections may also include aortic intramural haemorrhage and penetrating aortic ulcer (69).

Prompt aortic imaging by transoesophageal echocardiography, CT scan with intravenous contrast or MRI may confirm (or reasonably exclude) the diagnosis (69), and surgical



team consultation may be lifesaving. Concomitantly, medical therapy is mandatory to control heart rate (goal <60 beats/min), BP (goal between 100–120 mmHg) and pain (intravenous opiate analgesia), in an attempt to minimize further tension and damage to the aortic wall while waiting for surgery (37).

Treatment with rapid-acting and titratable intravenous beta-blockers (propranolol, metoprolol, labetalol or esmolol) is needed to first lower heart rate; in asthmatic patients non-dihydropyridine calcium channel antagonists may be used as an alternative. The combination with a vasodilator (intravenous sodium nitroprusside or nitroglycerin) may be necessary to effectively reduce BP. Beta-blockers should be initiated first to counteract reflex tachycardia and increased inotropy induced by vasodilators.

## CONCLUSION

The approach in the acute hypertensive setting is not yet well established. In asymptomatic patients who present to the ED with markedly elevated BP (including hypertensive urgencies and uncontrolled hypertensive patients), the optimal screening, treatment and follow-up interval, as related to the short-term and long-term clinical outcomes, need to be addressed in the future.

Treatment aspects of hypertensive emergencies and urgencies vary widely according to a patient's clinical conditions, and are largely based on experience rather than evidence. Therefore, it would be desirable to collect further, robust data in order to provide evidence-based recommendations on the diagnostic and therapeutic aspects of these conditions.

## REFERENCES

- Mancia G, Fagard R, Narkiewicz KJ et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; 34: 2159–2219.
- Chobanian AV, Bakris GL, Black HR et al. Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003; 42: 1206–1252.
- Whelton PK, Carey RM, Aronow WS et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Hypertension* 2018; 71(6): e13–e115.
- Shea S, Misra D, Ehrlich MH et al. Predisposing factors for severe, uncontrolled hypertension in an inner-city minority population. *N Engl J Med* 1992; 327: 776–781.
- Wolf SJ, Lo B, Shih RD et al. Clinical policy: Critical issues in the evaluation and management of adult patients in the emergency department with asymptomatic elevated blood pressure. *Ann Emerg Med* 2013; 62: 59–68.
- Vaughan CJ, Delanty N. Hypertensive emergencies. *Lancet* 2000; 356: 411–417.
- van den Born B-JH, Löwenberg EC, van der Hoeven NV et al. Endothelial dysfunction, platelet activation, thrombogenesis and fibrinolysis in patients with hypertensive crisis. *J Hypertens* 2011; 29: 922–927.
- Derhaschnig U, Testori C, Riedmueller E et al. Hypertensive emergencies are associated with elevated markers of inflammation, coagulation, platelet activation and fibrinolysis. *J Hum Hypertens* 2013; 27: 368–373.
- Shantsila A, Dwivedi G, Shantsila E et al. Persistent macrovascular and microvascular dysfunction in patients with malignant hypertension. *Hypertension* 2011; 57: 490–496.
- Agabiti-Rosei E, Salvetti M, Farsang C. European Society of Hypertension Scientific Newsletter: Treatment of hypertensive urgencies and emergencies. *J Hypertens* 2006; 24: 2482–2485.
- Kaplan NM. Management of hypertensive emergencies. *Lancet* 1994; 344(8933): 1335–1338.
- Perez Marco I, Musini Vijaya M, Wright James M. Effect of early treatment with anti-hypertensive drugs on short and long-term mortality in patients with an acute cardiovascular event. *Cochrane Database Syst Rev* 2009; (4): CD006743.
- Baron SL, Steege AL, Marsh SM et al. CDC health disparities and inequalities report—US, 2013. *MMWR. Surveill Summ* 2013; 62: 35–40.
- Varon J. Diagnosis and management of labile blood pressure during acute cerebrovascular accidents and other hypertensive crises. *Am J Emerg Med* 2007; 25: 949–959.
- Elliott WJ. Clinical features in the management of selected hypertensive emergencies. *Prog Cardiovasc Dis* 2006; 48: 316–325.
- Baumann BM, Cline DM, Pimenta E. Treatment of hypertension in the emergency department. *J Am Soc Hypertens* 2011; 5: 366–377.
- Katz JN, Gore JM, Amin A et al. Practice patterns, outcomes, and end-organ dysfunction for patients with acute severe hypertension: The Studying the Treatment of Acute hypertension (STAT) Registry. *Am Heart J* 2009; 158.
- Ponikowski P, Voors A, Anker S et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of. *Eur Soc Cardiol* 2016; 32: e1–641–e1–e61.
- Zampaglione B, Pascale C, Marchisio M, Cavallo-Perin P. Hypertensive urgencies and emergencies. Prevalence and clinical presentation. *Hypertension* 1996; 27: 144–147.
- Lane DA, Lip GYH, Beevers DG. Improving survival of malignant hypertension patients over 40 years. *Am J Hypertens* 2009; 22: 1199–1204.
- Edmunds BDGE, Lip GY. What has happened to malignant hypertension? A disease no longer vanishing. *J Hum Hypertens* 2000; 14: 171–174.
- Vlcek M, Bur A, Woisetschlager C et al. Association between hypertensive urgencies and subsequent cardiovascular events in patients with hypertension. *J Hypertens* 2008; 26: 657–662.
- Lip GY, Beevers M, Beevers G. The failure of malignant hypertension to decline: A survey of 24 years' experience in a multiracial population in England. *J Hypertens* 1994; 12: 1297–1305.
- Deshmukh A, Kumar G, Kumar N et al. Effect of joint national committee VII report on hospitalizations for hypertensive emergencies in the United States. *Am J Cardiol* 2011; 108: 1277–1282.
- Gore JM, Peterson E, Amin A et al. Predictors of 90-day readmission among patients with acute severe hypertension. The cross-sectional observational Studying the Treatment of Acute hypertension (STAT) study. *Am Heart J* 2010; 160.
- Patel KK, Young L, Howell EH et al. Characteristics and outcomes of patients presenting with hypertensive urgency in the office setting. *JAMA Intern Med* 2016; 176: 981.
- Grassi D, O'Flaherty M, Pellizzari M et al. Hypertensive urgencies in the emergency department: Evaluating blood pressure response to rest and to antihypertensive drugs with different profiles. *J Clin Hypertens* 2008; 10: 662–667.
- Mena G, Giraudon I, Alvarez E et al. Cocaine-related health emergencies in Europe: A review of sources of information, trends and implications for service development. *Eur Addict Res* 2013; 19: 74–81.
- Gandhi SK, Powers JC, Nomeir AM et al. The pathogenesis of acute pulmonary edema associated with hypertension. *N Engl J Med* 2001; 344: 17–22.
- Alam M, Zhang L, Stampehl M et al. Usefulness of speckle tracking echocardiography in hypertensive crisis and the effect of medical treatment. *Am J Cardiol* 2013; 112: 260–265.
- Muesan ML, Salvetti M, Paini A et al. Ocular fundus photography with a smartphone device in acute hypertension. *J Hypertens* 2017; 35: 1.
- Strandgaard S, Paulson OB. Cerebral blood flow and its pathophysiology in hypertension. *Am J Hypertens* 1989; 2: 486–492.
- Bannan LT, Beevers DG, Wright N. ABC of blood pressure reduction. *Br M J* 1980; 281(6249): 1200–1222.

34. Grossman E, Messerli FH, Grodzicki T, Kowey P. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? *JAMA* 2011; 276: 1328–1331.
35. Park SK, Kim WJ, Lee D-Y et al. Comparing the clinical efficacy of resting and antihypertensive medication in patients of hypertensive urgency: A randomized, control trial. *J Hypertens* 2017; 1.
36. Nielsen PE, Krogsgaard A, McNair A, Hilden T. Emergency treatment of severe hypertension evaluated in a randomized study: Effect of rest and furosemide and a randomized evaluation of chlorpromazine, dihydralazine and diazoxide Danish multicenter study. *Acta Med Scand* 1980; 208: 473–480.
37. Bossone E, LaBounty TM, Eagle KA. Acute aortic syndromes: Diagnosis and management, an update. *Eur Heart J* 2018; 39(9): 739–749d.
38. Brooks TWA, Finch CK, Lobo BL et al. Blood pressure management in acute hypertensive emergency. *Am J Health Syst Pharm* 2007; 64: 2579–2582.
39. Grise EM, Adeoye O, Lindsell C et al. Emergency department adherence to American Heart Association guidelines for blood pressure management in acute ischemic stroke. *Stroke* 2012; 43(2): 557–559.
40. Maisel AS, Peacock WF, McMullin N et al. Timing of immunoreactive B-Type natriuretic peptide levels and treatment delay in acute decompensated heart failure. An ADHERE (Acute Decompensated Heart Failure National Registry) analysis. *J Am Coll Cardiol* 2008; 52: 534–540.
41. Mebazaa A, Yilmaz MB, Levy P et al. Recommendations on pre-hospital & early hospital management of acute heart failure: A consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emer. *Eur J Heart Fail* 2015; 17: 544–558.
42. Rhoney D, Peacock WF. Intravenous therapy for hypertensive emergencies, part 1. *Am J Heal Pharm* 2009; 66: 1343–1352.
43. Matsue Y, Damman K, Voors AA et al. Time-to-furosemide treatment and mortality in patients hospitalized with acute heart failure. *J Am Coll Cardiol* 2017; 69: 3042–3051.
44. Felker Michael G. DOSE trial. *N Engl J Med* 2011; 364: 683–693.
45. Alexander P, Alkhwam L, Curry J et al. Lack of evidence for intravenous vasodilators in ED patients with acute heart failure: A systematic review. *Am J Emerg Med* 2015; 33: 133–141.
46. Ayaz S, Sharkey C, Kwiatkowski G et al. Intravenous enalaprilat for treatment of acute hypertensive heart failure. *Acad Emerg Med* 2014; 21: S260–S261.
47. Espinosa A, Ripollés-Melchor J, Casans-Francés R et al. Perioperative use of clevidipine: A systematic review and meta-analysis. *PLOS ONE* 2016; 11: 1–16.
48. Peacock WF, Chandra A, Char D et al. Clevidipine in acute heart failure: Results of the A Study of Blood Pressure Control in Acute Heart Failure—A Pilot Study (PRONTO). *Am Heart J* 2014; 167: 529–536.
49. Jauch EC, Saver JL, Adams HP et al. American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, Council on Clinical Cardiology, Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; 44: 870–947.
50. He J, Zhang Y, Xu T et al. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: The CATIS randomized clinical trial. *JAMA* 2014; 311: 479–489.
51. Lee M, Ovbiagele B, Hong K-S et al. Effect of blood pressure lowering in early ischemic stroke. *Stroke* 2015; 46: 1883–1889.
52. Xu T, Zhang Y, Bu X et al. He, Blood pressure reduction in acute ischemic stroke according to time to treatment. *J Hypertens* 2017; 35: 1244–1251.
53. Bath P, England T, Jarvis M et al. Rapid Intervention with Glyceryl Trinitrate in Hypertensive Stroke Trial-2 (RIGHT-2). *Int J Stroke* 2015; 10: 420–421.
54. Strbian D, Saposnik G. Review of the ENCHANTED Trial (Enhanced Control of Hypertension and Thrombolysis Stroke Study). *Stroke* 2016; 47: 3063–3064.
55. Anderson CS, Huang Y, Arima HE et al. Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage: The intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT). *Stroke* 2010; 41: 307–312.
56. Butcher KS, Jeerakathil T, Hill M et al. The intracerebral hemorrhage acutely decreasing arterial pressure trial. *Stroke* 2013; 44: 620–626.
57. Anderson CS, Heeley E, Huang Y et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med* 2013; 368: 2355–2365.
58. Qureshi AI, Palesch YY, Barsan WG et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med* 2016; 375: 1033–1043.
59. Carcel C, Wang X, Sato S et al. Degree and Timing of Intensive Blood Pressure Lowering on Hematoma Growth In Intracerebral Hemorrhage: Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial-2 Results. *Stroke* 2016; 47(6): 1651–1653.
60. Willmot M, Ghadami A, Whysall B et al. Transdermal glyceryl trinitrate lowers blood pressure and maintains cerebral blood flow in recent stroke. *Hypertension* 2006; 47: 1209–1215.
61. Anderson CS, Huang Y, Wang JG et al. Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT): A randomised pilot trial. *Lancet Neurol* 2008; 7: 391–399.
62. Garden A, Davey DA, Dommissie J. Intravenous labetalol and intravenous dihydralazine in severe hypertension in pregnancy. *Clin Exp Hypertens B* 1982; 1: 371–383.
63. Overgaard J, Skinhoj E. Paradoxical cerebral hemodynamic effect of hydralazine. *Stroke* 1975; 6: 402–404.
64. Peacock WF IV, Hilleman DE, Levy PD et al. A systematic review of nicardipine vs labetalol for the management of hypertensive crises. *Am J Emerg Med* 2012; 30: 981–993.
65. DeRyke LX, Janisse J, Coplin WM et al. A comparison of nicardipine and labetalol for acute hypertension management following stroke. *Neurocrit Care* 2008; 9: 167–176.
66. Roitberg BZ, Hardman J, Urbaniak K et al. Prospective randomized comparison of safety and efficacy of nicardipine and nitroprusside drip for control of hypertension in the neurosurgical intensive care unit. *Neurosurgery* 2008; 63: 115–120.
67. Narotam PK, Puri V, Roberts JM et al. Management of hypertensive emergencies in acute brain disease: Evaluation of the treatment effects of intravenous nicardipine on cerebral oxygenation. *J Neurosurg* 2008; 109: 1065–1074.
68. Liu-Deryke X, Levy PD, Parker DD et al. A prospective evaluation of labetalol versus nicardipine for blood pressure management in patients with acute stroke. *Neurocrit Care* 2013; 19: 41–47.
69. Hiratzka LF, Bakris GL, Beckman JA et al. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, Society for Vascular Medicine, 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, A. *Circulation* 2010; 121: e266–e369.



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# HYPERTENSION ASSOCIATED WITH PERIPHERAL ARTERY DISEASE

# 54

*Denis L. Clement*

## INTRODUCTION

It has repeatedly been recognized that physicians – both general practitioners and specialists – underestimate the impact of peripheral artery disease (PAD) on the prognosis of cardiovascular diseases. Physicians tend to forget that PAD by itself most often is due to atherosclerosis, which in many cases is a polyvascular disease. As a consequence, one should keep in mind that PAD, even when asymptomatic, carries a high risk for developing cardiovascular (CV) morbidity and mortality (1,2). Hypertension, when present in PAD patients, further increases such risk. Thus it is not difficult to understand why the total CV risk often is surprisingly high when PAD and hypertension coexist. Therefore, we should concentrate all our efforts to detect PAD in the population, especially when high blood pressure is also present.

This concept is further expanded in the present chapter, dealing particularly with the medical aspects of arterial disease in the lower extremity (recently also abbreviated as 'LEAD' [lower extremity arterial disease]) (3).

## CLINICAL ASPECTS

The symptoms of PAD have historically been categorized by Fontaine in Europe and further detailed by Rutherford in the United States (3). The most typical clinical picture in such patients is intermittent claudication: pain in the calf while walking; the pain disappears at rest. According to the Fontaine classification, intermittent claudication is class II. It should be mentioned that more and more atypical presentations occur, especially in female patients (Box 54.1).

Diagnosis of PAD is made by an association of complaints, palpation of pulses and by measuring the ankle-brachial index (ABI) (systolic blood pressure measured at the ankle divided by systolic pressure measured at the brachial artery). The lower the index, the more advanced is the occlusive process in the extremity. Values between 0.5 and 0.9 indicate light to moderate stenosis; however, at 0.5 critical limb ischaemia is present or likely to appear. The diagnosis can be further expanded by ultrasound imaging, and if interventional treatment is considered,

diagnosis can be expanded by arteriography, preferentially noninvasively.

In many patients, the symptoms vary or are not immediately recognizable; more importantly, the disease can remain completely asymptomatic. This can be due to the general condition of the patient not allowing them to perform any level of exercise (e.g. elderly patients with orthopaedic problems or patients with heart failure); another reason could be the presence of deep nerve disturbance such as in diabetes or other neurological disorders. Such condition has recently been called 'masked PAD' (3) in analogy to 'masked' hypertension.

Whatever the cause, it is very important to emphasize that asymptomatic patients are also at increased risk because as mentioned above, PAD in most patients is due to atherosclerosis. As a result, occlusive arterial disease should be searched for in all other vascular territories such as the coronary arteries, the carotid arteries or elsewhere in the body, especially in all patients likely to have atherosclerotic artery disease.

## PREVALENCE

Data on prevalence differ considerably depending on gender, age and criteria used to define PAD (4,5). If only the typical symptom of intermittent claudication is taken into account, a prevalence figure of 5% in the adult population is usually proposed. At the age of 70, it increases to at least 10%, according to the Rose Angina Questionnaire. However, as said above, many patients are asymptomatic or present with atypical symptoms that could significantly alter the figures on prevalence (Box 54.1).

Until recently, it was accepted that PAD is less prevalent in women (5). This is probably true in patients under 50 years but after this, prevalence significantly increases, and often worse cases are detected.

As far as the association of hypertension with PAD is concerned, data are surprisingly scarce. The general statement is that hypertension is accompanied by a two- to threefold increase in the risk of intermittent claudication (6–8); on the other hand, PAD patients often present with high blood pressure, especially systolic blood pressure, due to increased stiffening of the arteries (9).

**BOX 54.1 SUMMARY: SYMPTOMS AND PREVALENCE**

- The most typical symptom of PAD in the lower extremity is intermittent claudication.
- However, many patients are asymptomatic.
- In women and elderly patients, symptoms can be atypical and variable.
- Below the age of 50, prevalence is lower in women than in men; it sharply increases later, and often becomes more severe.

The best prevalence data are coming from the well documented Hungarian study run by Farkas (6); this study was performed on 21,892 hypertensive patients aged 50–75 years; ABI was systematically measured, and abnormal figures were found in 14.4% of the patients. The results of the prognostic part of this large study are anxiously awaited, as this could shed more light on the real risk these patients run.

Clearly there is ample room for improvement on our information on the prevalence of PAD in general, and on PAD associated with hypertension in particular.

**PROGNOSIS**

PAD as a manifestation of atherosclerosis is strongly linked to age, smoking, obesity, diabetes and lipids. New risk factors are regularly described; inflammation has recently been added to this list (10–12). The association with diabetes has very unfavourable consequences, as it impacts on both the proximal large arteries and on the distal small arteries, which can lead to profound ischaemia (Box 54.2).

There is ample information illustrating that PAD is accompanied by increased mortality and morbidity (1,2,13,14). This is the case in both symptomatic and asymptomatic patients (15). At 5 years, 20% of patients with intermittent claudication present with myocardial infarction (MI) or stroke; mortality is 10–15% (15–17).

Measuring the ABI is useful both for diagnosis of PAD and to estimate prognosis of PAD patients (3). An inverse relationship exists between the ABI and long-term prognosis, even after adjustment for several risk factors; an ABI below 0.90 is associated with a doubling of the 10-year rates of coronary events (15).

These generally accepted views on the prognosis of PAD patients were recently slightly amended by a meta-analysis (18); mean age in the cohorts ranged from 56–81 years; follow-up was 6.3 years. It was confirmed (18) that symptomatic PAD patients indeed present with higher 5-year

mortality compared to the reference population; however, it was striking that the local progression of the ischaemia is faster and more harmful than anticipated, as 4–27% of the critical ischaemia patients needed amputation.

Remarkably, data are coming out to show also that an *elevation* of the ABI index (above 1.3) may be accompanied by higher risk, which is most likely due to stiffening of the arteries. The figure representing ABI versus risk is thus not only J-like but rather U-shaped (13,19).

All these data clearly illustrate the very useful information that can be derived from measurement of ABI; the technique is easy, causing no pain or risk. It should be used in all patients at risk and especially those who already have gone through a vascular event like a coronary accident or a stroke. It also is very useful to detect early cases, allowing for better prevention and early treatment. The technique of ABI measurement should therefore be instructed also to vascular technicians, medical students and general practitioners.

**TREATMENT**

Treatment of the hypertensive patient with peripheral artery disease consists of treatment of risk factors in general, training (exercise therapy) and a pharmacological approach to both the arteries and the elevated blood pressure. For more advanced ischaemia, interventional treatment will be necessary; this is described in detail in a recent document (3). The final choice of treatment depends on the picture of the patient as a whole and after fully clarifying the local arterial condition. Also, the facilities and expertise of the centre should be considered. Finally, the personal choice of the patient after hearing all arguments available evidently plays the major role.

**RISK FACTOR CONTROL**

For both prevention and treatment, control of all regular risk factors plays an essential role in patients with PAD, known to have an elevated risk, as noted above. The importance of nutrition should be highlighted; it was documented by the National Health and Nutrition Examination Survey (NHANES) study (20) that improved nutrition is associated to a reduced prevalence of PAD in the United States. Management of such risk factors is described in detail in other parts of this book.

In this section we approach smoking cessation and training, control of lipids, antithrombotic treatment followed by drug treatment of intermittent claudication and control of high blood pressure by antihypertensive drugs.

**BOX 54.2 SUMMARY: RISK AND PROGNOSIS**

- PAD, even asymptomatic, carries a high risk for cardiovascular morbidity and mortality.
- Hypertension strongly increases the risk.
- Measurement of ABI is helpful to estimate prognosis, even after adjustment for all regular risk factors.

**SMOKING CESSATION AND TRAINING**

It is generally accepted that smoking cessation is essential both for the PAD symptoms as well as for short- and long-term prognosis. It has been documented for many years that simple exercise together with smoking cessation is often accompanied by improvement of walking distance (21). Exercises should not be complex: knee bending or toe elevation, performed three times a day, up to pain level, is capable of delaying the first pain; it is important that patients



**BOX 54.3 SUMMARY: TREATMENT**

- For both prevention and treatment, control of all regular risk factors is essential.
- Daily training, even with easy exercises, helps in increasing walking distance; it can be further improved by drug treatment.
- Smoking plays an important role in respect to symptoms of PAD.
- Control of lipids by lifestyle adaptation and statins should be strongly encouraged.
- Aspirin should be given to all symptomatic PAD patients unless contraindicated.

keep a log book wherein they take note of their daily activities; they should bring such log book to the consultation; it is very useful to see the changes made and even more, to stimulate them to continue their efforts (Box 54.3).

More intense exercise therapy can be provided in specialized centres; supervised exercise results in most cases in a greater improvement of walking distance than non-supervised training (22); however, this requires regular visits to a centre and can in most cases be given for short periods of time, like 6 weeks or a couple of months. Whatever the technique used, the easy exercises like toe elevation can often take over after the supervised training is stopped. Efficacy of training has also been documented by the results of the CLEVER (Claudication: Exercise versus Endoluminal Revascularization) study showing that supervised exercise improves walking capacity to a greater extent than intraluminal stenting (23). Smoking cessation is often helped by exercise therapy, and vice versa. A psychologist can effectively assist the patient. For most patients, adapted drug therapy to overcome their dependency on nicotine is necessary. Details are explained elsewhere (3).

**CONTROL OF LIPIDS**

Old and recent evidence has taught us that PAD patients often present with elevated lipid levels and that decreasing that level leads to better prognosis. This can be achieved by adapted food intake and in most cases, statin therapy. The goal is to bring L-cholesterol down to 70 mg% (1.8 mmol/L) or lower. The benefit of statin therapy to decrease CV events and total mortality was shown in randomized clinical trials (24) and was particularly striking in the Reduction of Atherothrombosis for Continued Health (REACH) (25). Combination with ezetimibe may further improve the results (26). The results obtained in the subgroup of PAD patients in the recent FOURIER trial of evolocumab, a monoclonal antibody to proprotein convertase subtilisin-kexin type 9 (PCSK9) (27), confirmed that decrease of L-cholesterol leads to reduction of CV events.

The mechanisms by which statins exert their beneficial effect is evidently by decreasing L-cholesterol levels, but pleiotropic mechanisms acting on the atherosclerotic process itself and the vascular wall may also be involved. If this is indeed the case, then one might reflect on using statins in these high-risk PAD patients even if L-cholesterol level

falls within normal limits; however, this has to be proven by studies specifically focused to the question.

**ANTITHROMBOTIC TREATMENT**

The beneficial effect of antithrombotic agents has convincingly been shown in *symptomatic* PAD patients; the most striking data come from the Antithrombotic Trialist Collaboration (28), where more than 6000 symptomatic PAD patients have been treated with aspirin and compared to controls; with aspirin, there was a significant decrease in major cardiovascular events (6.4 vs. 7.9%). In the Clopidogrel versus Aspirin study (CAPRIE) (29), at 3 years, clopidogrel was superior to aspirin in the subgroup of the large subgroup of symptomatic PAD patients. Although such results are quite convincing, it should be remembered that the difference between both these groups is not very large; also, one should not forget about the bleeding increase in patients treated with antithrombotic agents.

There is no clear evidence yet proving that aspirin should be administered to *asymptomatic* patients. However, based on the data given above, most investigators and the published guidelines accept that aspirin or clopidogrel should be given to all *symptomatic* PAD patients.

**DRUG TREATMENT OF INTERMITTENT CLAUDICATION**

Several drugs have been proposed to improve walking distance, but the results are variable; this is at least partially due to the techniques used to check walking distance. The three best tested drugs on the market are naftidrofuryl (30), which also improves quality of life (31), cilostazol, a phosphodiesterase inhibitor (22), and pentoxifylline. A systematic review and meta-analysis of these drugs (33) indicated that maximum walking distance increased with these drugs respectively by 60%, 25% and 11% relatively as compared to placebo; it was concluded that naftidrofuryl and cilostazol are both effective in the treatment of intermittent claudication. Although it appears logical that the results of training, smoking cessation and drug therapy are additive, objective information on it is scarce.

**ANTIHYPERTENSIVE TREATMENT**

Before all, it should be repeated that adaptation of life style and control of salt intake should be advised to all patients (34). All practical advice should be given and repeated regularly. It is useful in patients with hypertension combined with peripheral artery disease to verify whether the elevated blood pressure is dependent on secondary causes, especially renal artery stenosis, which is rather prevalent in this condition. This is particularly helpful in patients resistant to the usual antihypertensive drugs (Box 54.4).

There are no data proving that goal pressure should be different in hypertensive PAD patients compared to non-PAD patients. However, attention should be given to exaggerated pressure decrease in patients with critical limb ischaemia,

**BOX 54.4 SUMMARY: TREATMENT OF HYPERTENSION**

- Treatment of high blood pressure in PAD patients is largely similar to what is done in non-PAD patients.
- Control of lifestyle and risk factors is essential.
- Compliance to lifestyle adaptation and drug treatment should be carefully monitored long term.
- It is logical to give a preference to antihypertensive drugs that are accompanied by vasodilatation and increased local flow.
- Beta-blockers are not contraindicated in PAD patients with hypertension; on the contrary, they may be indicated in patients with compromised cardiac function.

as too much decrease in the central blood pressure might jeopardize their local unstable and critical condition.

There is no strict preference between the several antihypertensive drugs to be used in PAD patients. In general, they all can be used, and all are perfectly capable of controlling pressure. Also, none of them has a major influence on the symptoms of the occlusive disease.

Some points can help in making the choice. It is logical to give a preference to antihypertensive drugs that are accompanied by vasodilatation and increased local flow. ACE inhibitors, sartans and calcium antagonists are well positioned in this context. As soon as ACE inhibitors became available, their vasodilating capacity was shown. Later, the Heart Outcomes Prevention Trial (HOPE) (35) and the ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global endpoint Trial) study (36) demonstrated that ACE inhibitors and ARBs indeed decrease blood pressure and reduce CV events in PAD patients; limb outcome seemed not to be influenced in the favourable or in the adverse direction (37). In one study, a modest increase in walking capacity was demonstrated (38).

There has been a strong belief that beta-blockers could be harmful to the peripheral circulation. This is quite remarkable because even in the early days of beta-blockers, it was shown that the walking distance measured on the treadmill does not differ while taking beta-blockers, cardioselective or not, tested in a double-blind protocol versus placebo (39). On the contrary, beta-blockers may actually be an indication in patients with PAD and some degree of heart failure. Recently, metoprolol and nebivolol have been compared and shown to be well tolerated; in addition, in both groups, maximal walking distance improved significantly; with nebivolol (32) even initial walking distance ('first pain') improved.

**CONCLUSIONS**

Hypertension in patients with PAD carries a sharply increased total cardiovascular risk. All efforts should be made to control such risk. Measuring ABI is very helpful both for diagnosis and for estimating total CV risk. Great care should be taken to secure perfect compliance in the long term to all advice given. Training, even with easy

daily exercises, should be recommended. All antihypertensive drugs can be used to control of blood pressure. Beta-blockers are not contraindicated and may even help PAD patients with a compromised cardiac function.

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**CONFLICT OF INTEREST**

There is no conflict of interest to be declared.

**REFERENCES**

1. De Buyzere M, Clement DL. Management of hypertension in peripheral arterial disease. *Prog Cardiovasc Dis* 2008; 50: 238–263.
2. Clement DL, Boccalon H, Dormandy J et al. A Clinical approach to the management of the patient with coronary (Co) and/or carotid (Ca) artery disease who present with leg ischaemia (Lis). *Int Angiol* 2000; 19: 97–125.
3. Aboyans V, Ricco JB, Bartelink M et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J* 2018; 39(9): 763–816.
4. Duprez D. Natural history and evolution of peripheral obstructive arterial disease. *Int Angiol* 1992; 11: 165–168.
5. Hirsch AT, Allison MA, Gomes AS et al. A call to action: Women and peripheral artery disease. *Circulation* 2012; 125: 1449–1472.
6. Farkas K, Jarai Z, Kolossvary E et al. High prevalence of peripheral arterial disease in hypertensive patients. *J Hypertens* 2012; 30: 1526–1532.
7. Kannel WB, D'Agostino RB, Wilson PW et al. Diabetes, fibrinogen and risk of cardiovascular disease: The Framingham experience. *Am Heart J* 1990; 120: 672–676.
8. Fowkes FG, Hously E, Riemersma RA et al. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. *Am J Epidemiol* 1992; 135: 331–340.
9. Safar M, Priollet P, Luzy F et al. Peripheral arterial disease and isolated systolic hypertension: The ATTEST study. *J Hum Hypert* 2009; 23: 182–187.
10. Khawaja FJ, Kullo IJ. Novel markers of peripheral arterial disease. *Vasc Med* 2009; 14: 381–392.
11. Criqui MH, Denenberg LO, Ridker PM et al. Biomarkers in peripheral arterial disease patients and near- and longer-term mortality. *J Vasc Surg* 2010; 52: 85–90.
12. Ridker PM, Everett BM, Thuren T et al. for the Cantos group. Anti-inflammatory therapy with Canakinumab for atherosclerotic disease. *N Engl J Med* 2017; 377(12): 1119–1131.
13. Clement DL. Clinical management of patients presenting with hypertension and peripheral artery disease. *Manual Hypertens the European Soc Hypertens* 2014; 351–355.
14. Alberts MJ, Bhatt DL, Mas JL et al. Three year follow up and event rates in the international Reduction of Atherothrombosis for continued Health Registry (REACH). *Eur Heart J* 2009; 19: 2318–2326.
15. Fowkes FG, Murray GD, Butcher I. et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: A meta-analysis. *JAMA* 2008; 300: 197–208.
16. Bedenis R, Lethaby A, Maxwell H et al. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. *Cochrane Database Syst Rev* 2015; 2: CD000535.
17. Johnson WC, Williford WO. Benefits, morbidity, and mortality associated with long-term administration of oral anticoagulant therapy to patients with peripheral arterial bypass procedures: A prospective randomized study. *J Vasc Surg* 2002; 35: 413–421.

18. Sigvant B, Lundin F, Wahlberg E. The risk of disease progression in peripheral arterial disease is higher than expected: A meta-analysis of mortality and disease progression in peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2016; 51: 395–403.
19. Vlachopoulos C, Xaplanteris P, Aboyans V et al. The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: Endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. *Atherosclerosis* 2015; 241(2): 505–532.
20. Lane JS, Magno CP, Lane KT et al. Nutrition impacts the prevalence of peripheral arterial disease in the United States. *J Vasc Surg* 2008; 48: 897–904.
21. Clement DL. Occlusive arterial diseases in the lower limbs: Physiologic principles and guidelines to methods of investigation and treatment. *Int Angiol* 1984; 3: 57–65.
22. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med* 2001; 344: 1608–1621.
23. Murphy TP, Cutlip DE, Regensteiner JG et al. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: Six-month outcomes from the claudication: Exercise Versus Endoluminal Revascularization (CLEVER) study. *Circulation* 2012; 125: 130–139.
24. Antoniou GA, Fisher RK, Georgiadis GS et al. Statin therapy in lower limb peripheral arterial disease: Systematic review and meta-analysis. *Vasc Pharmacol* 2014; 63: 79–87.
25. Kumbhani DJ, Steg PG, Cannon CP et al. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: Insights from the REACH registry. *Eur Heart J* 2014; 35(41): 2864–2872.
26. Murphy SA, Cannon CP, Blazing MA et al. Reduction in total cardiovascular events with ezetimibe/simvastatin post-acute coronary syndrome: The IMPROVE-IT trial. *J Am Coll Cardiol* 2016; 67: 353–361.
27. Giugliano RP, Pedersen TR, Park JG et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: A prespecified secondary analysis of the FOURIER trial. *Lancet* 2017; 390(10106): 1962–1971.
28. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; 324: 71–86.
29. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; 348: 1329–1339.
30. Boccalon H, Leheret P, Mosnier M. [Effect of naftidrofuryl on physiological walking distance in patients with intermittent claudication.] [Article in French] *Ann Cardiol Angéiol* 2001; 50: 175–182.
31. Spengel F, Clement D, Boccalon H et al. Findings of the Naftidrofuryl in Quality of Life (NIQUOL) European Study program. *Int Angiol* 2002; 21: 20–27.
32. Espinola-Klein C, Weisser G, Jagodzinski A et al. Beta-blockers in patients with intermittent claudication and arterial hypertension: Results from the nebivolol or metoprolol in arterial occlusive disease trial. *Hypertension* 2011; 58: 148–154.
33. Stevens JW, Simpson E., Harnan S. et al. Systematic review of the efficacy of cilostazol, naftidrofuryl oxalate and pentoxifylline for the treatment of intermittent claudication. *Br J Surg* 2012; 99: 1630–1638.
34. Polonia J, Monteiro J, Almeida J et al. High salt intake is independently associated with a higher risk of cardiovascular events. A 12 years evaluation of a hypertensive cohort. *J Hypertens* 2015; 33(Suppl 1): e71.
35. Yusuf S, Sleight P, Pogue J et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; 342: 145–153.
36. Yusuf S, Teo KK, Pogue J et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; 358: 1547–1559.
37. Armstrong EJ, Chen DC, Singh GD et al. Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use is associated with reduced major adverse cardiovascular events among patients with critical limb ischemia. *Vasc Med* 2015; 20: 237–244.
38. Novo S, Abrignani MG, Pavone G et al. Effects of captopril and ticlopidine, alone or in combination, in hypertensive patients with intermittent claudication. *Int Angiol* 1996; 5: 169–174.
39. Bogaert M, Clement DL. Lack of influence of propranolol and metoprolol on walking distance in patients with chronic intermittent claudication. *Eur Heart J* 1983; 4: 203–204.



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Renata Cífková

## INTRODUCTION

Hypertensive disorders in pregnancy remain a major cause of maternal, fetal and neonatal morbidity and mortality not only in developing but also in developed countries. Pregnant women with hypertension are at higher risk for severe complications such as abruptio placentae, cerebrovascular accident, organ failure and disseminated intravascular coagulation. The fetus is at risk for intrauterine growth retardation, prematurity and intrauterine death. Hypertension is the most common medical problem in pregnancy; it may complicate 5–10% of pregnancies and accounts for approximately a quarter of all antenatal admissions. As women in developed countries currently delay childbirth, the impact of pre-existing hypertension will increase because the prevalence of hypertension increases with age. In 70% of cases, hypertension develops after 20 weeks' gestation, and only 30% of cases with hypertension are women with pre-existing hypertension.

## PHYSIOLOGICAL CHANGES IN BLOOD PRESSURE DURING PREGNANCY

Early in the first trimester, there is a fall in blood pressure (BP), caused by active vasodilatation due to the action of local mediators, such as prostacyclin and nitric oxide. This reduction in BP primarily affects diastolic BP (DBP), and a drop of 10 mmHg is usual by 13–20 weeks' gestation. BP continues to fall until 20–24 weeks when a nadir is reached. After this, there is a gradual increase in BP until term, when pre-pregnancy levels are achieved. This BP fluctuation occurs in both normotensive and hypertensive women.

Women with pre-existing hypertension tend to have even greater decreases in their BP in early pregnancy, and their 'normal' rise in the third trimester may be misdiagnosed as gestational hypertension. Women with DBP of 75 mmHg or systolic BP (SBP) of 120 mmHg in mid-pregnancy, or 85 mmHg DBP or 130 mmHg SBP in later pregnancy, should be monitored closely (1).

Immediately after delivery, BP usually falls, then increases over the first 5 postnatal days. Even women whose BP was normal throughout pregnancy may experience transient hypertension in the early postpartum period, perhaps reflecting a degree of vasomotor instability. A summary of changes in major hemodynamic parameters is given in Table 55.1.

## BP MEASUREMENT

It is essential to confirm high BP readings, preferably on two occasions (2), at least 15 minutes apart in severe hypertension (i.e.  $\geq 160/110$  mmHg in the obstetric literature).

Blood pressure in pregnancy should be measured in the sitting position (or the left lateral recumbent during labour) with an appropriately sized arm cuff at heart level. Supine positioning is usually associated with lower BP values and left lateral positioning may provide the lowest values because the right arm is frequently elevated above heart level during BP measurement (3).

Mercury sphygmomanometers are still the gold standard for BP measurement in pregnancy. Automated devices tend to under-record the true BP values and are unreliable in severe pre-eclampsia. Mean reported differences have been as great as 15 mmHg when compared with mercury sphygmomanometry, and 25 mmHg when compared with intra-arterial measurements, with wide variation (4).

As mercury sphygmomanometers have been eliminated from many institutions, BP can be measured using automated (usually oscillometric) BP devices, which have been validated according to standardized protocols, specifically in pregnancy and pre-eclampsia (see: <http://www.dableducational.org>) (5).

Korotkoff phase V is now recommended for the measurement of DBP in pregnancy (6–8). If Korotkoff sounds persist as the level approaches 0 mmHg, then the point of muffling of the sound is used (phase IV) to indicate the DBP.

Several ambulatory BP monitoring (ABPM) devices have been successfully validated specifically for use in pregnancy and used to generate normal ranges for ABPM



**Table 55.1** Cardiovascular changes in pregnancy

| Parameter                | Change           | Timing                                                                         |
|--------------------------|------------------|--------------------------------------------------------------------------------|
| Systolic blood pressure  | ↓4–6 mmHg        | All bottom at 20–24 weeks, then rise gradually to pre-pregnancy values at term |
| Diastolic blood pressure | ↓8–15 mmHg       |                                                                                |
| Mean arterial pressure   | ↓6–10 mmHg       |                                                                                |
| Heart rate               | ↑12–18 beats/min | Early 2nd trimester, then stable                                               |
| Stroke volume            | ↑10–30%          | Early 2nd trimester, then stable                                               |
| Cardiac output           | ↑33–45%          | Peaks in early 2nd trimester, then until term                                  |

throughout gestation. Clinical application of ABPM has been assessed in three main areas: white-coat hypertension, early prediction of pre-eclampsia, and prognostic assessment of hypertension in later pregnancy. As white-coat hypertension is a common phenomenon in pregnant women who appear to be hypertensive according to routine BP measurement early in pregnancy, ABPM might be useful in the initial assessment to avoid unnecessary anti-hypertensive treatment (9). On the other hand, hypertension in pregnancy, as diagnosed by ABPM, has been shown to be associated with lower birth weights (10,11), and is superior to the office measurement of BP in predicting the outcome of pregnancy (12–14). Ambulatory BP monitoring is a better predictor of proteinuria, pre-term delivery, and low birth weight (13,14). It is therefore clinically useful in high-risk pregnant women with hypertension, or in those with diabetic or hypertensive nephropathy (15).

## DEFINITION OF HYPERTENSION IN PREGNANCY

The definition of hypertension in pregnancy was not uniform for a long time (2,16,17). It used to include an elevation in BP during the second trimester from a baseline reading in the first trimester, or to pre-pregnancy levels, but a definition based on absolute BP values (SBP  $\geq 140$  mmHg or DBP  $\geq 90$  mmHg) is now preferred (2,17).

Most of the obstetric literature distinguishes mild and severe hypertension rather than grades used by the European Society of Hypertension and the European Society of Cardiology (ESH-ESC; 2,8).

## CLASSIFICATION OF HYPERTENSION IN PREGNANCY

Hypertension in pregnancy is not a single entity but comprises (2,8,18):

- Pre-existing hypertension
- Gestational hypertension
- Pre-existing hypertension plus superimposed gestational hypertension with proteinuria
- Antenatally unclassifiable hypertension

## PRE-EXISTING HYPERTENSION

Pre-existing hypertension complicates 1–5% of pregnancies and is defined as BP  $\geq 140/90$  mmHg that either pre-dates pregnancy or develops before 20 weeks of gestation. Hypertension usually persists more than 42 days postpartum. It may be associated with proteinuria.

However, there are several caveats to the diagnosis of pre-existing hypertension. Women with undiagnosed mild hypertension may appear normotensive in early pregnancy because of the normal fall of BP commencing in the first trimester. This may mask the pre-existing hypertension, and when hypertension is recorded later in pregnancy it may be interpreted as gestational. Sometimes the diagnosis is only made several months postpartum when the BP fails to normalize as would be expected with gestational hypertension.

## GESTATIONAL HYPERTENSION

Gestational hypertension is pregnancy-induced hypertension, with or without proteinuria, complicating 6–7% of pregnancies and developing only after 20 weeks of gestation; it is characterized by poor organ perfusion and usually resolves within 42 days postpartum. Gestational hypertension associated with significant proteinuria ( $>0.3$  g/24 h in a 24-h urine collection or  $\geq 30$  mg/mmol urinary creatinine in a spot random urine sample) is known as pre-eclampsia.

Pre-eclampsia is a pregnancy-specific syndrome that occurs after mid-gestation, defined by de novo appearance of hypertension, accompanied by new-onset proteinuria. It is a systemic disorder with both maternal and fetal manifestations. Pre-eclampsia was classically defined as a triad of hypertension, oedema and proteinuria, but oedema is no longer considered part of the diagnostic criteria, as it occurs in up to 60% of normal pregnancies and is no longer included because of the lack of specificity. Overall, pre-eclampsia complicates 5–6% of pregnancies, but this figure increases to up to 25% in women with pre-existing hypertension. Risk factors for developing pre-eclampsia are given in Table 55.2.

Pre-eclampsia remains one of the three most frequently cited causes of maternal death and is responsible for an estimated 64,000 deaths a year worldwide (19). Developing countries have had persistently higher rates of

**Table 55.2** Risk factors for developing pre-eclampsia

|                                                    |
|----------------------------------------------------|
| Nulliparity                                        |
| Multiple pregnancy                                 |
| Family history of pre-eclampsia                    |
| Chronic hypertension                               |
| Diabetes                                           |
| Increased insulin resistance                       |
| Increased body mass index                          |
| Hypercoagulability (inherited thrombophilia)       |
| Renal disease even without significant impairment  |
| Low socioeconomic status                           |
| Antiphospholipid syndrome (acquired thrombophilia) |
| Previous pre-eclampsia                             |
| Hydatidiform mole                                  |
| Black ethnicity                                    |

maternal and child mortality due to pre-eclampsia compared with developed countries. While the immunological and genetic alterations are relevant in the development of pre-eclampsia in developed countries, nutritional, metabolic and infectious factors are largely responsible for the high incidence of pre-eclampsia in developing countries. In the United States, the rate of pre-eclampsia increased by 40% between 1990 and 1994, probably as a consequence of increasing maternal age and multiple births, factors predisposing to pre-eclampsia (20).

The risks to the fetus from pre-eclampsia include growth restriction secondary to placental insufficiency and premature delivery. Pre-eclampsia is one of the most common causes of prematurity, accounting for 25% of all infants with very low birth weight, <1500 g; it is also associated with an increased incidence of cardiovascular disease in later life in mothers and babies (21,22). A paternal, but not maternal, history of essential hypertension is associated with increased risk of hypertension in children, the risk being greater in daughters than sons. Pregnancy may thus unveil or exacerbate this effect, possibly reflecting underlying endothelial vulnerability (23).

The main feature of pre-eclampsia is impaired perfusion to virtually every organ of the body. There is vasospasm and activation of platelets and the coagulation system resulting in the formation of microthrombi. The link between the placenta and the systemic disorder appears to involve endothelial dysfunction and oxidative stress. Symptoms and signs of severe pre-eclampsia include right upper quadrant/epigastric pain due to liver oedema ± hepatic haemorrhage; headache ± visual disturbance (cerebral oedema); occipital lobe blindness; hyperreflexia ± clonus; and convulsions (cerebral oedema). Management of pre-eclampsia essentially focuses on recognition of the condition and ultimately delivery of the placenta, which is curative.

As proteinuria may be a late manifestation of pre-eclampsia, it is advised to be suspicious when *de novo* hypertension is accompanied by headache, abdominal pain, or abnormal laboratory tests, specifically low platelet count and abnormal liver enzymes, and it is recommended to treat such patients as pre-eclamptic.

The pathophysiology of pre-eclampsia can be divided into two stages: alterations in placental perfusion (stage 1)

and maternal syndrome (stage 2). The placenta is the key component of pregnancy that leads to pre-eclampsia. The reduced placental perfusion is primarily due to abnormalities in implantation and vascular remodelling (24). In normal pregnancy, the spiral arteries that perfuse the placenta undergo remarkable remodelling from small muscular arteries in the pregnant state to significantly distended vessels that have lost both their smooth muscle and inner elastic lamina layers. This extensive remodelling does not occur in pre-eclampsia. There may be some superficial remodelling, but it never extends beyond the decidual lining, whereas in normal pregnancy, the modified vessels extend into the inner third of the myometrium (25). Many vessels in pre-eclamptic women undergo no remodelling, and this results in reduced placental perfusion. It is now evident that these interactions include precisely regulated expression molecules involved in attachment and invasion in response to environmental and maternal signals, and that this process is impaired in pre-eclampsia (26). Several conditions associated with macrovascular disease such as hypertension, diabetes and collagen vascular diseases also increase the risk of pre-eclampsia, leading to speculation that impaired placental perfusion may be the common denominator. Obstetric conditions associated with large placentas (hydatidiform mole, hydropic placentas, and placentas with multiple gestations) all increase the risk of pre-eclampsia (27). It is proposed that, in these large placentas, there is a relative reduction in placental perfusion. Another alteration of the spiral arteries in pre-eclampsia, atherosclerosis, results in occlusion of the decidual vessels reminiscent of the vascular findings of allograft rejection supporting an immunological component of pre-eclampsia (28).

Stage 2, the maternal syndrome, begins when the plasma volume is reduced, with decreased blood flow to organs other than placenta, resulting in hemoconcentration, haemorrhage and necrosis (29). In the liver, evidence can be found of reduced perfusion with secondary necrosis and haemorrhage. In the heart, subendocardial necrosis similar to that seen in hypovolemic shock can occur. The explanation for systematically reduced perfusion includes vasoconstriction, microthrombi and reduced plasma volume secondary to loss of fluid from the vascular compartment. The vasoconstriction is not attributable to increased endogenous pressors, but rather to an increased sensitivity to virtually all circulating pressor agents. Pre-eclampsia is also characterized by activation of the coagulation cascade. Renal biopsy specimens from women with pre-eclampsia reveal a change seen in no other form of hypertension. Termed glomeruloendotheliosis, the lesion consists primarily of enlargement of the glomerulus caused by hypertrophy of endothelial cells. Numerous markers of endothelial activation are present in the circulation of pre-eclamptic women weeks to months before clinically evident disease (30). Vessels from women with pre-eclampsia manifest reduced endothelium-mediated relaxation and plasma or serum from pre-eclamptic women can adversely alter endothelial function *in vitro* either with cells in culture or intact vessels.

There is a considerable amount of evidence supporting the role of angiogenic factors in triggering pre-eclampsia (tyrosine-like soluble factor, and soluble endoglin) (31). These molecules bind to angiogenic proteins such as VEGF and prevent them from joining their membrane receptors on endothelial cells leading to endothelial dysfunction.

These factors are elevated about 6–8 weeks before the clinical manifestation of pre-eclampsia and their plasma concentrations are related to the severity of disease (32).

Women destined to develop pre-eclampsia have lower placental growth factor (PlGF) levels and higher soluble fms-like tyrosine kinase-1 (sFlt-1) than women with normal pregnancies (33). Changes in the circulating concentrations of these parameters precede the onset of pre-eclampsia. A ratio of sFlt-1/PlGF  $\leq 38$  can be used to exclude the development of pre-eclampsia in the next week when suspected clinically (34).

### PRE-EXISTING HYPERTENSION PLUS SUPERIMPOSED GESTATIONAL HYPERTENSION WITH PROTEINURIA

Pre-existing hypertension is associated with further worsening of BP and protein excretion  $\geq 3$  g/day in 24-h urine collection after 20 weeks' gestation; it corresponds to the previous terminology 'chronic hypertension with superimposed pre-eclampsia'.

### ANTENATALLY UNCLASSIFIABLE HYPERTENSION

This is hypertension with or without systemic manifestation, if BP was first recorded after 20 weeks' gestation. Reassessment is necessary at or after 42 days postpartum. If hypertension is resolved by then, the condition should be reclassified as gestational hypertension with or without proteinuria. If the hypertension is not resolved by then, the condition should be reclassified as pre-existing hypertension.

## RECOMMENDED LABORATORY INVESTIGATIONS

Hypertensive disorders in pregnancy, particularly gestational hypertension with or without proteinuria, may produce changes in the hematologic, renal and hepatic profiles that may adversely affect prognosis and both neonatal and maternal outcomes.

Basic laboratory investigations recommended for monitoring patients with hypertension in pregnancy are presented in Table 55.3. All pregnant women should be assessed for proteinuria and early pregnancy to rule out pre-existing renal disease and, in the second half of pregnancy, to screen for pre-eclampsia. A positive dipstick test ( $\geq +$ ) should prompt further investigations, including an albumin-to-creatinine ratio (ACR), which can be quickly determined in a single spot urine sample.

Some authors (35) recommend ultrasound investigation of the adrenals and urine metanephrine and normetanephrine assays in all pregnant women with hypertension, as pheochromocytoma may be completely asymptomatic, and if not diagnosed before labour, fatal.

Determination of the sFlt-1-to-PlGF ratio is now widely available to rule out the development of pre-eclampsia in the next week when suspected clinically (33,34).

## PHEOCHROMOCYTOMA IN PREGNANCY

A pheochromocytoma in pregnancy is one of the most life-threatening conditions for the mother and fetus. Although extraordinarily rare, with a frequency of 0.002% of all pregnancies, this tumour is notorious for its devastating consequences (36). As in nonpregnant patients, the signs

**Table 55.3** Basic laboratory investigations recommended for monitoring patients with hypertension in pregnancy

|                                        |                                                                                                                                                                                                                                                                                                 |
|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hemoglobin and hematocrit              | Hemoconcentration supports diagnosis of gestational hypertension with or without proteinuria. It indicates severity. Levels may be low in very severe cases because of hemolysis.                                                                                                               |
| Platelet count                         | Low levels $<100,000 \times 10^9/L$ may suggest consumption in the microvasculature. Levels correspond to severity and are predictive of recovery rate in postpartum period, especially for women with HELLP syndrome.                                                                          |
| Serum AST, ALT                         | Elevated levels suggest hepatic involvement. Increasing levels suggest worsening severity.                                                                                                                                                                                                      |
| Serum LDH                              | Elevated levels are associated with haemolysis and hepatic involvement. May reflect severity and may predict potential for recovery postpartum, especially for women with HELLP syndrome.                                                                                                       |
| Urinalysis                             | Dipstick test for proteinuria has significant false-positive and false-negative rates. Positive dipstick results ( $\geq 1$ ) should prompt further investigations including albumin/creatinine ratio. Negative dipstick results do not rule out proteinuria, especially if DBP $\geq 90$ mmHg. |
| Urinary albumin/creatinine (ACR)       | Can be quickly determined in a single-spot urine sample; a value $<30$ mg/mmol can reliably rule out proteinuria in pregnancy. Values $\geq 30$ mg/mmol identify significant proteinuria.                                                                                                       |
| Proteinuria (24-hour urine collection) | Standard to quantify proteinuria, but often inaccurate. If in excess of 2 g/day, very close monitoring is warranted. If in excess of 3 g/day, delivery should be considered.                                                                                                                    |
| Serum uric acid                        | Elevated levels aid in differential diagnosis of gestational hypertension and may reflect severity.                                                                                                                                                                                             |
| Serum creatinine                       | Levels drop in pregnancy. Elevated levels suggest increasing severity of hypertension; assessment of 24-hour creatinine clearance may be necessary.                                                                                                                                             |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HELLP, Hemolysis, Elevated Liver enzyme levels, and Low Platelet count; LDH, lactate dehydrogenase.

and symptoms are quite variable but not specific, with hypertension being one of the most prominent signs. If undiagnosed, maternal and fetal mortality is around 50%; on the other hand, early detection and proper treatment during pregnancy decrease the maternal and fetal mortality to <5 and <15%, respectively. For the biochemical diagnosis, plasma or urinary metanephrines are the test of choice since they have the highest sensitivity and the highest negative predictive value. For reliable localization, magnetic resonance imaging is the most suitable technique, with a sensitivity of more than 90%. When a pheochromocytoma is diagnosed, it should be removed by laparoscopic adrenalectomy after 10–14 days of drug pretreatment as in nonpregnant patients (alpha-adrenoreceptor blockade combined with beta-adrenergic blockade started some days later). If the pheochromocytoma is diagnosed in the third trimester, the patient should be managed until the fetus is viable using the same drug regimen as for regular surgical preparation. Cesarean section with tumour removal in the same session or at later stage is then preferred, since vaginal delivery is possibly associated with higher mortality.

## MANAGEMENT OF HYPERTENSION IN PREGNANCY

The majority of women with pre-existing hypertension in pregnancy have mild to moderate hypertension (140–179/90–109 mmHg) and are at low risk for cardiovascular complications within the short time frame of pregnancy. Women with essential hypertension and normal renal function have good maternal and neonatal outcomes; they are candidates for non-drug therapy because there is no evidence that pharmacological treatment results in improved neonatal outcome. Some women with treated pre-existing hypertension are able to stop their medication in the first half of pregnancy because of the physiological fall in BP during this period. However, close monitoring and if necessary, resumption of treatment, are essential.

There are not sufficient data regarding treatment of hypertension in pregnancy, as pharmaceutical companies have been reluctant to test drugs in this small market with a high potential of litigation. Childbearing potential without reliable contraception is an exclusion criterion in basically all clinical trials testing antihypertensive drugs. Pharmaceutical companies are not willing to take any, even a small risk, and as no data are available for most of the antihypertensive drugs marketed over the last 20 years, the vast majority of newer antihypertensive drugs is strictly contraindicated in pregnancy.

The only trial of treatment of hypertension in pregnancy with adequate infant follow-up (7.5 years) was performed more than 30 years ago with alpha-methyldopa, now rarely used in nonpregnant women (37,38). Past clinical trials also have not supported a beneficial effect on pregnancy outcome of treating mild hypertension. There has been no reduction in perinatal mortality, placental abruption, or superimposed pre-eclampsia (39,40). All these trials are subject to criticism, including small numbers, starting the drug too late in pregnancy, or flawed study design; however, no other data are available. These studies have led to recommendations to treat only on the basis of BP sufficiently elevated to pose a potential acute risk to the

mother (41). Small and frequently poorly designed studies have recently suggested that therapy of mildly elevated BP may prevent progression to pre-eclampsia (42,43). Even for women with BP elevation sufficient to justify therapy for their own benefit, it is not clear whether it is beneficial for or detrimental to the fetus. In several studies, treatment of hypertensive women resulted in an increased risk of growth restriction in their infants (44). It is not known whether this is the inevitable consequence of lower BP during pregnancy or if it is due to excessive pressure decreases or too specific drugs.

## NON-PHARMACOLOGICAL MANAGEMENT AND PREVENTION OF HYPERTENSION IN PREGNANCY

Non-pharmacological management (45) of hypertension in pregnancy has a limited role because randomized studies of dietary and lifestyle interventions showed only minimal effects on pregnancy outcomes. A short-term hospital stay may be required for confirming the diagnosis of and ruling out severe gestational hypertension (pre-eclampsia), in which the only effective treatment is delivery. Management, depending on BP, gestational age and presence of associated maternal and fetal risk factors, includes close supervision, limitation of activities and some bed rest in the left lateral position.

A normal diet without salt restriction is advised, particularly close to delivery, as salt restriction may induce a low intravascular volume. Increased energy and protein intake are not beneficial in the prevention of gestational hypertension. Although weight reduction may be helpful in reducing BP in nonpregnant women, it is not recommended during pregnancy in obese women, as weight reduction can be associated with reduced neonatal weight and slower subsequent growth in infants of dieting obese mothers.

However, as maternal obesity can result in negative outcomes for both women and fetuses, guidelines for healthy ranges of weight gain in pregnancy have been established. In pregnant women with normal body mass index (BMI <25 kg/m<sup>2</sup>), the recommended weight gain is 11.2–15.9 kg; for overweight pregnant women (BMI 25.0–29.9 kg/m<sup>2</sup>) it is 6.8–11.2 kg; and for obese pregnant women (BMI ≥30 kg/m<sup>2</sup>) the recommended weight gain is <6.8 kg (46).

Regular exercise might be continued with caution.

Calcium supplementation (1.5–2 g orally) is recommended for prevention of pre-eclampsia in women with low dietary calcium intake (<600 mg/d) (47) from the first antenatal clinic visit.

In a multicentre randomized clinical trial of effect of fish oil in a high-risk population of pregnant women with pregnancy complications, fish oil supplementation delayed the onset of delivery in low and middle, but not in high, fish consumers (48).

Fish oil supplementation as well as vitamin and nutrient supplements have no role in the prevention of hypertensive disorders. Some studies with vitamin C and vitamin E supplementation were associated with more frequent low birth-weight (<2.5 kg) and adverse perinatal outcome (49–52).

There has been considerable controversy regarding the efficacy of low-dose aspirin for the prevention of pre-eclampsia. Despite a large meta-analysis reporting a small



benefit of aspirin in preventing pre-eclampsia (53), two other analyses came to opposing conclusions. Rossi and Mullin used pooled data from approximately 5000 women at high risk and 5000 at low risk for pre-eclampsia and reported no effect of low-dose aspirin in the prevention of the disease (54). Bujold et al., however, pooled data from over 11,000 women enrolled in RTCs of low-dose aspirin in pregnant women and concluded that women who initiated treatment at <16 weeks of gestation had a significant and marked reduction of the relative risk for developing pre-eclampsia (relative risk: 0.47) and severe pre-eclampsia (relative risk: 0.09) compared with controls (55). The ASPRA (Aspirin for Evidence-based Pre-eclampsia Prevention) trial showed that 150 mg of aspirin compared with placebo resulted in a lower incidence of pre-eclampsia (56). Thus, women at high or moderate risk of pre-eclampsia should be advised to take 100–150 mg of aspirin daily from weeks 12–36.

High risk of pre-eclampsia includes any of the following:

- Hypertensive disease during a previous pregnancy
- Chronic kidney disease
- Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
- Type 1 or type 2 diabetes
- Chronic hypertension

Moderate risk of pre-eclampsia includes  $\geq 1$  of the following risk factors:

- First pregnancy
- Age 40 years or older
- Pregnancy interval of more than 10 years
- Body mass index (BMI) of 35 kg/m<sup>2</sup> or more at first visit
- Family history of pre-eclampsia
- Multiple pregnancy

## PHARMACOLOGICAL MANAGEMENT OF HYPERTENSION IN PREGNANCY

The value of continued administration of antihypertensive drugs to pregnant women with chronic hypertension continues to be an area of debate. While there is a consensus that drug treatment of severe hypertension in pregnancy is required and beneficial (57), treatment of less severe hypertension is controversial. Although it might be beneficial for the mother with hypertension to reduce her BP, lower BP may impair uteroplacental perfusion and thereby jeopardize fetal development. Much uncertainty about the benefits of BP lowering in pregnant women with mild pre-existing hypertension stems from published trials too small to detect a modest reduction in obstetric complications.

All antihypertensive drugs have either been shown or are assumed to cross the placenta and reach the fetal circulation. However, none of the antihypertensive agents in routine use have been documented to be teratogenic, although angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists, and aliskiren, a direct renin inhibitor, are fetotoxic.

While the goal of treating hypertension is to reduce maternal risk, the agents selected must be efficacious and safe for the fetus (6,58).

## TREATMENT OF SEVERE HYPERTENSION

While there is no agreement on the definition of severe hypertension in pregnancy (with values ranging between 160–180 mmHg/>110 mmHg), there is a consensus that SBP  $\geq 170$  or DBP  $\geq 110$  mmHg in a pregnant woman should be considered an emergency, and hospitalization is absolutely essential (8). The selection of the antihypertensive drug and its route of administration depend of the expected time of delivery. Pharmacological treatment with intravenous labetalol, oral methyldopa or nifedipine is to be initiated. Intravenous hydralazine should no longer be thought of as the drug of choice as its use is associated with more perinatal adverse effects than other drugs (59). However, hydralazine is still commonly used when other treatment regimens have failed to achieve adequate BP control, as for most obstetricians, its side effect profile is acceptable. Prolonged treatment with sodium nitroprusside is associated with an increased risk of fetal cyanide poisoning, as nitroprusside is metabolized into thiocyanate excreted into urine (60). Therefore, sodium nitroprusside should be reserved for extreme emergencies and used for the shortest period of time possible.

The drug of choice in pre-eclampsia associated with pulmonary oedema is nitroglycerin (given as intravenous infusion of 5 µg/min, gradually increased every 3–5 min to a maximum dose of 100 µg/min).

## TREATMENT OF MILD TO MODERATE HYPERTENSION

The benefits of antihypertensive therapy for mildly to moderately elevated BP in pregnancy (<160/110 mmHg) have not been demonstrated in clinical trials. Recent reviews including a Cochrane analysis concluded there are insufficient data to determine the benefits and risks of antihypertensive therapy for mild to moderate hypertension (defined as 140–169 mmHg SBP and 90–109 mmHg DBP) (62–64). Of note, with antihypertensive treatment there seems to be less risk of developing hypertension (risk ratio 0.50 with a number-needed-to-treat of 10), but no difference in outcomes of pre-eclampsia, neonatal death, preterm birth and small-for-gestational-age babies with treatment (61).

In the absence of randomized controlled trials, recommendations can only be guided by expert opinion. International and national guidelines vary with respect to thresholds for starting treatment and BP targets in pregnancy. The suggestion in the 2007 ESH/ESC Guidelines (65) of considering drug treatment in all pregnant women with persistent elevation of BP >150/95 mmHg is supported by more recent US data, which show an increasing trend in the rate of pregnancy-related hospitalizations with stroke – especially during the postpartum period – from 1994–2007 (66), and by an analysis of stroke victims with severe pre-eclampsia and eclampsia (67). Despite lack of evidence, the 2013 Task Force reconfirms that physicians should consider early initiation of antihypertensive treatment at values >140/90 mmHg in women with (i) gestational hypertension (with or without proteinuria), (ii) pre-existing hypertension with the superimposition of



**Table 55.4** Antihypertensive drugs used in pregnancy

*Women with pre-existing hypertension are advised to continue their current medication except for ACE inhibitors, angiotensin II antagonists and aliskiren.*

|                          |                                                                                                                                                  |
|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Methyldopa               | Drug of choice                                                                                                                                   |
| Labetalol                | Has comparable efficacy with methyldopa; in the case of severe hypertension, it could be given intravenously.                                    |
| Calcium-channel blockers | Oral nifedipine or IV isradipine could be given in hypertensive emergencies. Potential synergism with magnesium sulphate may induce hypotension. |

*Abbreviations:* ACE, angiotensin-converting enzyme; IV, intravenous.

gestational hypertension or (iii) hypertension with asymptomatic organ damage (OD) or symptoms at any time during pregnancy.

For non-severe hypertension (Table 55.4), methyldopa, labetalol, and calcium antagonists (most data available for nifedipine) are the drugs of choice. Beta-blockers appear to be less effective than calcium antagonists and may induce fetal bradycardia, growth retardation and hypoglycemia; the type and dose should be carefully selected, with atenolol best avoided (Table 55.5) (68). Calcium channel blockers are considered to be safe if not given concomitantly with magnesium sulphate (risk of hypotension due to potential synergism). ACE inhibitors, angiotensin II antagonists, and aliskiren should not be used in pregnancy. Women with pre-existing hypertension may continue their current antihypertensive medication except for RAS blockers. The plasma volume is reduced in pre-eclampsia; diuretic therapy is therefore inappropriate unless there is oliguria when low-dose furosemide may be considered. Magnesium sulphate IV is recommended for the prevention of eclampsia and treatment of seizures (69).

**Table 55.5** Antihypertensive drugs contraindicated in pregnancy or to be used with caution

|                                                                     |                                                                                                                                                                          |
|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ACE inhibitors, angiotensin II antagonists, direct renin inhibitors | Fetal abnormalities including death can be caused and these drugs should not be used in pregnancy.                                                                       |
| Diuretics                                                           | Diuretics are recommended for chronic hypertension if prescribed before gestation or if patients appear to be salt-sensitive. They are not recommended in pre-eclampsia. |
| Direct vasodilators                                                 | Hydralazine is no longer the parenteral drug of choice because of its perinatal adverse effects.                                                                         |
| Beta-blockers                                                       | Metoprolol appears to be safe and effective in late pregnancy; it should be avoided in early pregnancy; because of fetotoxicity, atenolol is contraindicated.            |

*Abbreviation:* ACE, angiotensin-converting enzyme.

## DELIVERY

Induction of delivery is appropriate in pre-eclampsia with visual disturbances, coagulation abnormalities or fetal distress. In asymptomatic gestational hypertension or asymptomatic mild pre-eclampsia, delivery is recommended at 37 weeks (70).

## BP POSTPARTUM

Postpartum hypertension is common. BP usually rises over the first 5 days after delivery. Women experiencing hypertension during pregnancy may be normotensive after birth but then become hypertensive again in the first postnatal week. The need to obtain hypertensive control may delay discharge. Methyldopa should be avoided postpartum because of the risk of postnatal depression.

## HYPERTENSION AND LACTATION

Breastfeeding does not increase BP in nursing mothers. Bromocriptin, which is still used to suppress lactation in some countries, may induce hypertension. All antihypertensive agents taken by the nursing mother are excreted into breast milk. Most of the antihypertensive drugs are present at very low concentrations, except for propranolol and nifedipine, whose concentrations in breast milk are similar to those in maternal plasma.

## RISK OF RECURRENCE OF HYPERTENSIVE DISORDERS IN A SUBSEQUENT PREGNANCY

Women experiencing hypertension in their first pregnancy are at increased risk in a subsequent pregnancy. The earlier the onset of hypertension in the first pregnancy, the greater the risk of recurrence.

## LONG-TERM CARDIOVASCULAR CONSEQUENCES IN PREGNANCY-INDUCED HYPERTENSION

Women who develop gestational hypertension or pre-eclampsia are at increased risk of hypertension and stroke in later adult life (71). Furthermore, there is evidence of an increased risk of ischaemic heart disease in women who experience pre-eclampsia or isolated intrauterine growth retardation together with increased death from ischaemic heart disease (72). Therefore, it is of utmost importance that all women with pregnancy-induced hypertension have their BP measured annually.

Endothelial dysfunction and early alteration of carbohydrate and lipid metabolism are present in otherwise healthy women with previous gestational hypertension. These abnormalities, along with a relative hyperandrogenism,

could explain, at least in part, the increased risk for cardiovascular disease in later life in these women (73).

On the other hand, women who go through pregnancy without developing hypertension are at reduced risk of becoming hypertensive in later life when compared to nulliparous women. Thus, pregnancy may offer a window into the future cardiovascular health of women that is unavailable in men.

## REFERENCES

- Lindheimer MD, Akbari A. Hypertension in pregnant women. In: Oparil S, Weber MA (eds). *Hypertension: A Companion to Brenner and Rector's The Kidney*. WB Saunders, Philadelphia; 2000, 688–701.
- Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1281–1357.
- Wichman K, Rydén G, Wichman M. The influence of different positions and Korotkoff sounds on the blood pressure measurements in pregnancy. *Acta Obstet Gynecol Scand Suppl* 1984; 118: 25–28.
- Villar J, Say L, Shennan A et al. Methodological and technical issues related to the diagnosis, screening, prevention, and treatment of pre-eclampsia and eclampsia. *Int J Gynaecol Obstet* 2004; 85(Suppl 1): S28–S41.
- Reinders A, Cuckson AC, Lee JT et al. An accurate automated blood pressure device for use in pregnancy and pre-eclampsia: The Microlife 3BTO-A. *BJOG* 2005; 112(7): 915–120.
- Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. NIH Publication No. 00-3029; originally printed 1990; revised July 2000. *Am J Obstet Gynecol* 2000 183(1): S1–S22.
- Higgins JR, de Swiet M. Blood pressure measurement and classification in pregnancy. *Lancet* 2001; 357: 131–135.
- Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: The Task Force on the management of cardiovascular diseases during pregnancy of the European Society of Cardiology (ESC). *Eur Heart J* 2011; 32: 3147–3197.
- Brown MA, Mangos G, Davis G et al. The natural history of white coat hypertension during pregnancy. *Int J Obstet Gynaecol* 2005; 112: 601–606.
- Churchill D, Perry IJ, Beevers DG. Ambulatory blood pressure in pregnancy and fetal growth. *Lancet* 1997; 349: 7–10.
- Waugh J, Perry IJ, Halligan AW et al. Birth weight and 24-hour ambulatory blood pressure in nonproteinuric hypertensive pregnancy. *Am J Obstet Gynecol* 2000; 183: 633–637.
- Bellomo G, Narducci PL, Rondoni F et al. Prognostic value of 24-hour blood pressure in pregnancy. *JAMA* 1999; 282: 1447–1452.
- Penny JA, Halligan AWE, Shennan AH et al. Automated, ambulatory or conventional blood pressure measurement in pregnancy: Which is the better predictor of severe hypertension? *Am J Obstet Gynecol* 1998; 178: 521–526.
- Peek M, Shennan AH, Halligan A et al. Hypertension in pregnancy: Which method of blood pressure measurement is most predictive of outcome? *Obstet Gynecol* 1996; 88: 1030–1033.
- Staessen JA, Asmar R, De Buyzere M et al. Task Force II: Blood pressure measurement and cardiovascular outcome. *Blood Press Monit* 2001; 6: 355–370.
- Consensus Report. National high blood pressure education program working group report on high blood pressure in pregnancy. *Am J Obstet Gynecol* 1990; 63: 1689–1712.
- Levine RJ, Ewell MG, Hauth JC et al. Should the definition of pre-eclampsia include a rise in diastolic blood pressure of >90mmHg in association with proteinuria? *Am J Obstet Gynecol* 2000; 183: 787–792.
- Helewa ME, Burrows RF, Smith J et al. Report of the Canadian Hypertension Society Consensus Conference: 1. Definitions, evaluation and classification of hypertensive disorders in pregnancy. *Can Med Assoc* 1997; 157: 715–725.
- De Brouwere V, van Lerberghe W. *Safe Motherhood Strategies: A Review of the Evidence*. ITG Press, Antwerp; 2001.
- Ventura SJ, Martin JA, Curtin SC et al. Births: Final data for 1999. *Natl Vital Stat Reports* 2001; 49: 1–100.
- Irgens HU, Reisater L, Irgens LM et al. Long term mortality of mothers and fathers after pre-eclampsia: Population-based cohort study. *BMJ* 2001; 323: 1213–1217.
- Hiatt AK, Brown HL, Britton KA. Outcome of infants delivered between 24 and 28 weeks' gestation in women with severe pre-eclampsia. *J Matern Fetal Med* 2001; 10: 301–314.
- The Genetics of Pre-eclampsia (GOPEC) Consortium. Babies, pre-eclamptic mothers and grandparents: A three-generation phenotyping study. *J Hypertens* 2007; 25: 849–854.
- Roberts JM. Pregnancy related hypertension. In: Creasy RK, Resnik R (eds.) *Maternal Fetal Medicine*. 4th ed. WB Saunders, Philadelphia; 1998, 833–872.
- Pijnenborg R, Anthony J, Davey DA et al. Placental bed spiral arteries in the hypertensive disorders of pregnancy. *Br J Obstet Gynaecol* 1991; 98: 648–655.
- Zhou Y, Genbacev O, Damsky CH et al. Oxygen regulates human cytotrophoblast differentiation and invasion: Implications for endovascular invasion in normal pregnancy and in pre-eclampsia. *J Reprod Immunol* 1998; 39: 197–213.
- Page EW. The relation between hydatid moles, relative ischemia of the gravid uterus, and the placental origin of eclampsia. *Am J Obstet Gynecol* 1939; 37: 291–293.
- Labarrere CA. Acute atherosclerosis: A histopathological hallmark of immune aggression? *Placenta* 1988; 9: 95–108.
- Roberts JM, Pearson G, Cutler J et al. Summary of the NHBRI Working Group on research on hypertension during pregnancy. *Hypertension* 2003; 41: 437–445.
- Roberts JM. Endothelial dysfunction in pre-eclampsia. *Semin Reprod Endocrinol* 1998; 16: 5–15.
- Wang A, Rana S, Karumanchi SA. Preeclampsia: The role of angiogenic factors in its pathogenesis. *Physiology (Bethesda)* 2009; 24: 147–158.
- Kendall RL, Thomas KA. Inhibition of vascular endothelial cell growth factor activity by an endogenously encoded soluble receptor. *Proc Natl Acad Sci USA* 1993; 90: 10705–10709.
- Leanos-Miranda A, Campos-Galicia I, Isordia-Salas I et al. Changes in circulating concentrations of soluble fms-like tyrosine kinase-1 and placental growth factor measured by automated electrochemiluminescence immunoassays methods are predictors of preeclampsia. *J Hypertens* 2012; 30(11): 2173–2181.
- Zeisler H, Llorba E, Chantraine F et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. *N Engl J Med* 2016; 374(1): 13–22.
- Rossi GP, Seccia TM, Pessina AC. Clinical use of laboratory tests for the identification of secondary forms of arterial hypertension. *Crit Rev Clin Lab Sci* 2007; 44: 1–85.
- Lenders JW. Pheochromocytoma and pregnancy: A deceptive connection. *Eur J Endocrinol* 2012 February; 166(2): 143–150.
- Redman CW. Fetal outcome in trial of antihypertensive treatment in pregnancy. *Lancet* 1976; 2: 753–756.
- Cockburn J, Moar VA, Ounsted M et al. Final report of study on hypertension during pregnancy: The effects of specific treatment on the growth and development of the children. *Lancet* 1982; 1: 647–649.
- Umans JG, Lindheimer MD. Antihypertensive therapy in pregnancy. *Curr Hypertens Rep* 2001; 3: 392–399.
- Abalos E, Duley L, Steyn DW et al. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2018; CD002252.
- Gifford RW, August PA, Cunningham G et al. Report of the national high blood pressure education program working group on high blood pressure in pregnancy. *Am J Obstet Gynecol* 2000; 183: S1–S22.
- Pickles CJ, Broughton Pipkin F et al. A randomised placebo controlled trial of labetalol in the treatment of mild to moderate pregnancy induced hypertension. *Br J Obstet Gynaecol* 1992; 99: 964–968.
- Blake S, MacDonald D. The prevention of the maternal manifestations of pre-eclampsia by intensive antihypertensive treatment. *Br J Obstet Gynaecol* 1991; 98: 244–248.
- Von Dadelszen P, Ornstein MP, Bull SB et al. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: A meta-analysis. *Lancet* 2000; 355: 87–92.
- Dodd JM, Turnbull D, McPhee AJ et al. Antenatal lifestyle advice for women who are overweight or obese: LIMIT randomised trial. *BMJ* 2014; 348: g1285.
- Leddy MA, Power ML, Schulkin J. The impact of maternal obesity on maternal and fetal health. *Rev Obstet Gynecol* 2008; 1: 170–178.

47. Hofmeyr GJ, Lawrie TA, Atallah AN et al. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst Rev* 2014; (6): CD001059.
48. Olsen SF, Osterdal ML, Salvig JD et al. Duration of pregnancy in relation to fish oil supplementation and habitual fish intake: A randomised clinical trial with fish oil. *Eur J Clin Nutr* 2007; 61(8): 976–985.
49. Xu H, Perez-Cuevas R, Xiong X et al. An international trial of antioxidants in the prevention of preeclampsia (INTAPP). *Am J Obstet Gynecol* 2010; 202(3): 239 e1–239 e10.
50. Villar J, Purwar M, Merialdi M et al. World Health Organisation multicentre randomised trial of supplementation with vitamins C and E among pregnant women at high risk for pre-eclampsia in populations of low nutritional status from developing countries. *BJOG* 2009; 116(6): 780–788.
51. Spinnato JA, 2nd, Freire S, Pinto ESJL et al. Antioxidant therapy to prevent preeclampsia: A randomized controlled trial. *Obstet Gynecol* 2007; 110(6): 1311–1318.
52. Poston L, Briley AL, Seed PT et al. Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): Randomised placebo-controlled 4555 trial. *Lancet* 2006; 367(9517): 1145–1154.
53. Duley L, Henderson-Smith D, Knight M et al. Antiplatelet drugs for prevention of preeclampsia and its consequences: Systematic review. *BMJ* 2001; 322: 329–333.
54. Rossi AC, Mullin PM. Prevention of pre-eclampsia with low-dose aspirin or vitamins C and E in women at high or low risk: A systematic review with meta-analysis. *Eur J Obstet Gynecol Reprod Biol* 2011; 158: 9–16.
55. Bujold E, Roberge S, Lacasse Y et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: A meta-analysis. *Obstet Gynecol* 2010; 116: 402–414.
56. Rolnik DL, Wright D, Poon LC et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med* 2017; 377(7): 613–622.
57. Khedun SM, Moodley J, Naicker T et al. Drug management of hypertensive disorders of pregnancy. *Pharmacol Ther* 1997; 74: 221–258.
58. Dekker G, Sibai BM. Primary, secondary, and tertiary prevention of pre-eclampsia. *Lancet* 2001; 357: 209–215.
59. Magee LA, Cham C, Waterman EJ et al. Hydralazine for treatment of severe hypertension in pregnancy: Meta-analysis. *BMJ* 2003; 327: 955–960.
60. Coppage KH, Sibai BM. Treatment of hypertensive complications in pregnancy. *Curr Pharm Des* 2005; 11: 749–759.
61. Abalos E, Duley L, Steyn D et al. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2007; CD002252.
62. von Dadelszen P, Magee LA. Antihypertensive medications in management of gestational hypertension-preeclampsia. *Clin Obstet Gynecol* 2005; 48: 441–459.
63. Magee LA, Ornstein MP, von Dadelszen P. Fortnightly review: Management of hypertension in pregnancy. *BMJ* 1999; 318: 1332–1336.
64. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2014; (2): CD002252.
65. Mancia G, De Backer G, Dominiczak A et al. 2007 Guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; 25: 1105–1187.
66. Kuklina EV, Tong X, Bansil P et al. Trends in pregnancy hospitalizations that included a stroke in the United States from 1994 to 2007: Reasons for concern? *Stroke* 2011; 42: 2564–2570.
67. Martin JN Jr, Thigpen BD, Moore RC et al. Stroke and severe pre-eclampsia and eclampsia: A paradigm shift focusing on systolic blood pressure. *Obstet Gynecol* 2005; 105: 246–254.
68. Lydakis C, Lip GYH, Beevers M et al. Atenolol and fetal growth in pregnancies complicated by hypertension. *Am J Hypertens* 1999; 12: 541–247.
69. The Magpie Trial Collaborative Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie trial: A randomised placebo-controlled trial. *Lancet* 2002; 359: 1877–1890.
70. Koopmans CM, Bijlenga D, Groen H et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): A multicentre, open-label randomised controlled trial. *Lancet* 2009; 374(9694): 979–910.
71. Wilson BJ, Watson MS, Prescott GJ et al. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: Results from cohort study. *BMJ* 2003; 326: 845–851.
72. Jonsdottir LS, Arngrimsson R, Geirsson RT et al. Death rates from ischemic heart disease in women with a history of hypertension in pregnancy. *Acta Obstet Gynecol Scand* 1995; 74: 772–776.
73. Paradisi G, Biaggi A, Savone R et al. Cardiovascular risk factors in healthy women with previous gestational hypertension. *J Clin Endocrinol Metab* 2006; 91: 1233–1238.



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## INTRODUCTION

Drug-induced hypertension is an important secondary cause of hypertension which is often overlooked. The incidence approaches 100% for some drugs, and many effects are dose-dependent. With the increasing availability of nonprescription (over-the-counter) medications and herbal remedies, drug-induced elevations in blood pressure (BP) are likely to be more widespread. Drugs can lead to *de novo* hypertension, worsening of pre-existing hypertension, and even hypertensive crises. Clinicians are therefore well advised to actively question patients about any agents that could impact upon BP control including use of herbal medicines and over-the-counter preparations, along with their regular medication profile.

Drug-induced elevations in BP are often the result of multiple pathophysiological mechanisms. Determining the pathophysiology can help decide which antihypertensive agent is likely to be the most beneficial when it is not possible to stop the offending drug (Table 56.1). Where the drug can be discontinued, the elevation in BP usually normalises, although not always, which will contribute to a higher lifetime cardiovascular risk. This may necessitate a period of ongoing surveillance for months or years.

## SYSTEMIC CORTICOSTEROIDS

Synthetic corticosteroids have multiple uses ranging from topical application for skin rashes to the treatment of cancer. The hypertensive stimulant depends on the amounts of mineralocorticoid and glucocorticoid contained within the steroid (1). Mineralocorticoids lead to hypertensive effects through sodium retention, whereas glucocorticoids are thought to enhance vascular reactivity towards vasoconstrictor substances. Synthetic corticosteroids have less mineralocorticoid activity compared with cortisol but will still cause BP to rise. One in five patients on high doses of corticosteroids (greater than 80 mg/day) will develop hypertension (2,3). This is a dose-dependent effect and elevations in BP can be seen within 24 hours. Fluoroprednisolone and 9- $\alpha$ -fluorocortisol have direct mineralocorticoid activity, and at high doses result in arterial hypertension,

hypokalaemia, metabolic alkalosis and pseudohypoaldosteronism. Carbenoxolone and liquorice (which contains glycyrrhizic acid) lead to a similar clinical picture from inhibiting 11 $\beta$ -hydroxysteroid dehydrogenase resulting in more glucocorticoids being converted to mineralocorticoids. Other mechanisms have also been implicated in corticosteroid-induced hypertension such as PPAR- $\alpha$  dependent mechanisms. Dexamethasone increases BP (systolic and diastolic) by means of an increase in peripheral resistance (3,4). Corticosteroids should be stopped where possible or minimum doses used. Where they cannot be stopped, diuretics and dietary salt restriction form the mainstay of management.

## ANALGESICS

Meta-analyses have reported that nonsteroidal anti-inflammatory drugs (NSAIDs), induce elevations in BP of around 4–5 mmHg and reduce the efficacy of various antihypertensive medication (5–8). Chronic NSAID use in patients with coronary artery disease is associated with increased mortality, nonfatal myocardial infarction, and nonfatal stroke (9). NSAIDs inhibit both cyclooxygenase-1 (COX1) and cyclooxygenase-2 (COX2), which leads to alterations in prostaglandin synthesis. In particular, prostaglandin-E2 and prostaglandin-I2, both implicated in vasodilation and renal sodium excretion, are reduced. Various other mechanisms are involved including salt and water retention, increased vascular resistance and enhanced synthesis of renal endothelin-1 (7). These effects are more pronounced in patients with chronic kidney disease. The greatest elevations are seen with ibuprofen (6.5 mmHg), indomethacin (4.7 mmHg), naproxen (6.1 mmHg) and piroxicam (6.2 mmHg) (6,5,10,11). Selective COX-2 inhibitors such as the discontinued drugs rofecoxib and celecoxib, also lead to dose-dependent elevations in BP through similar mechanisms (12–15). Management should include calcium channel blockers (CCBs) and centrally acting antihypertensive agents, which are less affected by NSAIDs. Diuretics are also helpful, but care has to be taken as they may worsen renal hypoperfusion, which may elevate BP further. Acetaminophen (paracetamol) is generally regarded as not having any effect on BP but it has been



**Table 56.1** Summary of drugs leading to hypertension based on the pathophysiology

| Drug                                                                                                                                                                                        | Pathway                                                                                                                                                                              | Risk factors                                                                                                                                                                                                                          | Management                                                                                                                                                              |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Direct vasoconstriction</i>                                                                                                                                                              |                                                                                                                                                                                      |                                                                                                                                                                                                                                       |                                                                                                                                                                         |
| <b>Chemotherapeutic agents</b><br>Bevacizumab<br>Sunitinib<br>Lapatinib<br>Sorafenib<br>Axitinib<br>Pazopanib                                                                               | VEGF or tyrosine kinase inhibition reducing NO production                                                                                                                            |                                                                                                                                                                                                                                       | Dihydropyridine CCBs<br>ACEI<br>Avoid verapamil, diltiazem and nifedipine                                                                                               |
| <b>Immunosuppressants</b><br>Ciclosporin                                                                                                                                                    | <ul style="list-style-type: none"> <li>■ Multiple factors including decreased NO</li> <li>■ Systemic and renal vasoconstriction</li> <li>■ Salt and fluid retention</li> </ul>       | <ul style="list-style-type: none"> <li>■ Pre-existing hypertension</li> <li>■ Concurrent corticosteroids</li> <li>■ Co-prescription with erythromycin</li> <li>■ Poor renal function</li> </ul>                                       | Discontinuation may not lead to a reduction in BP levels<br>CCBs (caution as some lead to paradoxical increase in ciclosporin levels)<br>Alternative immunosuppressants |
| <i>Sodium resorption and fluid retention</i>                                                                                                                                                |                                                                                                                                                                                      |                                                                                                                                                                                                                                       |                                                                                                                                                                         |
| <b>Analgesics/anti-inflammatory</b><br>NSAIDs<br>Rofecoxib<br>Celecoxib<br>Acetaminophen                                                                                                    | Inhibition of COX-1 and COX-2 and reduced prostaglandin synthesis                                                                                                                    | Renal impairment                                                                                                                                                                                                                      | CCBs<br>Centrally acting agents<br>Diuretics<br>(May blunt effects of ACEI/A2RB)                                                                                        |
| <b>Corticosteroids</b><br><i>Glucocorticoids</i><br><i>Mineralocorticoids</i><br>Liquorice<br>Carbenoxolone<br>9- $\alpha$ fluoroprednisolone<br>9- $\alpha$ fluorocortisol<br>Ketoconazole | Mineralocorticoid receptor activation                                                                                                                                                | Pre-existing hypertension                                                                                                                                                                                                             | Use lowest dose/short duration<br>Diuretics<br>ACEI/A2RB<br>Mineralocorticoid receptor antagonists<br>Dietary salt restriction                                          |
| <b>Sex hormones</b><br>Oestrogen and progestin<br>Testosterone and other androgens<br>Danazol                                                                                               | Increased angiotensin II leading to aldosterone generation and mineralocorticoid receptor activation<br>Androgen receptor agonism                                                    | <ul style="list-style-type: none"> <li>■ Hypertension during pregnancy</li> <li>■ Family history of hypertension</li> <li>■ Raised body mass index</li> <li>■ Diabetes mellitus</li> <li>■ Illicit anabolic steroid use</li> </ul>    | Discontinuation<br>ACEI or A2RBs (outweigh potential pregnancy risk)<br>Diuretics                                                                                       |
| <i>Sympathomimetics</i>                                                                                                                                                                     |                                                                                                                                                                                      |                                                                                                                                                                                                                                       |                                                                                                                                                                         |
| <b>Antidepressants</b><br>Venlafaxine<br>TADs<br>Fluoxetine                                                                                                                                 | Increased norepinephrine and SNS activity                                                                                                                                            | <ul style="list-style-type: none"> <li>■ Age</li> <li>■ Male gender</li> </ul>                                                                                                                                                        | Try alternative if possible<br>Use lowest dose                                                                                                                          |
| <b>HAART</b>                                                                                                                                                                                | <ul style="list-style-type: none"> <li>■ Likely multifactorial</li> <li>■ Adipose tissue redistribution associated with enhanced SNS activity and RAAS activation (87–89)</li> </ul> | <ul style="list-style-type: none"> <li>■ Increasing age</li> <li>■ Increasing BMI</li> <li>■ Duration of HAART treatment</li> <li>■ Higher systolic and cholesterol levels pre-treatment</li> <li>■ Low starting CD4 count</li> </ul> | Centrally acting drugs<br>$\beta$ -blockers<br>$\alpha$ -blockers<br>ACEI/A2RB                                                                                          |
| <b>Anaesthetic related</b><br>Ketamine<br>Fentanyl<br>Physostigmine<br>Scopolamine                                                                                                          | SNS activation                                                                                                                                                                       | <ul style="list-style-type: none"> <li>■ Gender</li> <li>■ Polymorphism of norepinephrine transporter gene (90)</li> </ul>                                                                                                            | Centrally acting drugs<br>$\beta$ -blockers<br>$\alpha$ -blockers                                                                                                       |
| <b>Decongestants</b><br>Phenylephrine<br>Pseudoephedrine<br>Oxymetazoline                                                                                                                   | Stimulate $\alpha$ -1-receptors on smooth muscle leading to vasoconstriction                                                                                                         | Baroreflex failure                                                                                                                                                                                                                    | Avoid if possible                                                                                                                                                       |

(Continued)

**Table 56.1 (Continued)** Summary of drugs leading to hypertension based on the pathophysiology

| Drug                                                         | Pathway                                                                                                                                                                                                       | Risk factors                                                                                                            | Management                                                                                                         |
|--------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| <b>Appetite suppressants</b>                                 |                                                                                                                                                                                                               |                                                                                                                         |                                                                                                                    |
| Sibutramine                                                  |                                                                                                                                                                                                               |                                                                                                                         |                                                                                                                    |
| <b>ADHD therapy</b><br>Dexmethylphenidate<br>Methylphenidate |                                                                                                                                                                                                               |                                                                                                                         | Use lowest possible doses<br>Drug holiday in ADHD<br>Behavioural therapies in ADHD<br>Guanfacine with ADHD therapy |
| <b>Herbal supplements</b><br>Ephedra<br>Bitter orange        |                                                                                                                                                                                                               |                                                                                                                         |                                                                                                                    |
| <b><math>\beta</math>-3 agonists</b><br>Mirabegron           | Stimulation of cardiovascular $\beta$ -3 adrenergic receptors                                                                                                                                                 |                                                                                                                         | Contraindicated in uncontrolled HTN. BP check before starting and at regular intervals after                       |
| Cocaine<br>Amphetamines                                      | Prevents peripheral reuptake of norepinephrine                                                                                                                                                                | <ul style="list-style-type: none"> <li>■ Intranasal administration</li> <li>■ Pre-existing hypertension</li> </ul>      | Benzodiazepines<br>Nitroglycerin<br>IV nitroprusside<br>IV phentolamine                                            |
| Caffeine                                                     | <ul style="list-style-type: none"> <li>■ SNS stimulation</li> <li>■ Enhances catecholamine release</li> <li>■ Suppresses adenosine</li> </ul>                                                                 | Low caffeine exposure                                                                                                   | Limit intake                                                                                                       |
| <i>Other drugs</i>                                           |                                                                                                                                                                                                               |                                                                                                                         |                                                                                                                    |
| <b>Recombinant human erythropoietin</b>                      | <ul style="list-style-type: none"> <li>■ Increases calcium in vascular smooth muscle cells</li> <li>■ RAAS activation</li> <li>■ Increased ET-1</li> <li>■ Decreased NO Increased vasoconstriction</li> </ul> | <ul style="list-style-type: none"> <li>■ Pre-existing hypertension</li> <li>■ Family history of hypertension</li> </ul> | Diuretics<br>Haemodialysis<br>Venesection in refractory cases                                                      |
| <b>Alcohol</b>                                               | <ul style="list-style-type: none"> <li>■ SNS stimulation</li> <li>■ RAAS activation</li> <li>■ Increased vasoconstriction</li> </ul>                                                                          | Heavy consumption                                                                                                       | Reduction in intake<br>Diuretics<br>Mineralocorticoid receptor antagonists                                         |

associated with a pressor effect and subsequent hypertension in a number of studies, including patients with coronary artery disease (16,17).

## SEX HORMONES

The combined oral contraceptive pill results in hypertension in 5% of users. The minimum amounts of hormones at which this is seen is 50 mg oestrogen and 1–4 mg progestins (18). However, even lower doses of the combined oral contraceptive pill (containing 20–35 mg of oestrogens) can increase BP by 8 mmHg (19). Elevations in BP leading to hypertensive crises have also been reported. Risk factors predisposing to the development of hypertension include hypertension during pregnancy, a family history of hypertension, elevated body mass index, and diabetes mellitus (18). The underlying mechanism is related to increased hepatic angiotensinogen production and its downstream effects with eventual aldosterone activation of the mineralocorticoid receptors (20). This is not the only effect, however, as spironolactone alone is not enough to control the elevations in BP. It is postulated that high-dose

oestrogens also act directly on mineralocorticoid receptors and influence 11- $\beta$ -hydroxysteroid dehydrogenase activity. Discontinuation usually sees the BP returning to baseline over a number of weeks, but it can take over 6 months. If antihypertensive agents are needed, then angiotensin converting enzyme inhibitors (ACEIs) or angiotensin-2 receptor blockers (A2RBs) are useful but their use needs to be outweighed by the risk of potential pregnancy and fetal abnormalities. BP elevations are not seen with hormone-replacement therapy and the progesterone-only pill (21).

Testosterone leads to androgen receptor agonism, which will elevate BP through the resulting salt and volume retention. This is not seen when testosterone is given to men with hypogonadism. Indeed, in this group, BP improves by 23/16 mmHg and there is a reduction in cardiovascular risk (22). Anabolic androgenic steroids are synthetic molecules derived from testosterone and are used in various medical conditions. They are also used by people to enhance exercise performance and for cosmetic reasons. They can lead to hypertension and other cardiovascular abnormalities; for example, left ventricular dysfunction, aortic stiffness and atherosclerosis (23,24). Aortic stiffness may persist years after discontinuation of androgens, leading to increased cardiovascular risk (24). Taurine helps to

attenuate these effects in animal models (23). Danazol is a semisynthetic androgen used in the management of endometriosis and hereditary angioedema. It is also a performance-enhancing drug misused by exercise enthusiasts. It can lead to elevated BP, which resolves on discontinuation.

## CHEMOTHERAPEUTIC AGENTS AND IMMUNOSUPPRESSANTS

Cancer patients are now living longer and are likely to die from non-cancer-related illnesses, including cardiovascular disease (25). The recognition and management of both cardiovascular risk and disease in these patients is therefore becoming more important. Of all the comorbid conditions, hypertension is the most frequent in patients with cancer (25–27). Chemotherapeutic agents that are commonly associated with hypertension include alkylating agents, demethylation inhibitors and vascular endothelial growth factor (VEGF) inhibitors (27,28). Of the alkylating agents, cyclophosphamide, isophosphamide, cisplatin and busulfan have all been associated with hypertension. VEGF is a heparin-binding glycoprotein with high affinity for endothelial cells. The VEGF inhibitors can be divided into two groups, both of which can induce hypertension: the VEGF monoclonal antibody bevacizumab, and small molecules that inhibit tyrosine kinase (normally stimulated by VEGF), such as sunitinib and sorafenib. It is not surprising that these drugs lead to hypertension, as both VEGF and tyrosine kinase are involved in modulation of vascular function through nitric oxide regulation. Other putative pathophysiological mechanisms include induction of rarefaction of the microvasculature, loss of antioxidative effects, activation of endothelin-1, sodium retention, stimulation of the sympathetic nervous system (SNS) activity, increased production of vasoconstrictors and activation of the renin–angiotensin–aldosterone system (RAAS) (29,30). The overall result is endothelial dysfunction and changes in the microvasculature.

The overall incidence of hypertension is 32% using VEGF inhibitors (31). VEGF inhibitors are associated with grade 3 or higher hypertension in 10–20% of patients at the starting dose (31). Bevacizumab leads to hypertension in 17–31% of patients (31,32). It can result in *de novo* hypertension in 22% and worsening of hypertension in 18.7% (33). Hypertensive crises occur in 1% and include reversible posterior leukoencephalopathy syndrome (34). The median time to develop hypertension is 131 days (range 7–316 days) (35). In comparison, sorafenib leads to hypertension in 23.4% (severe hypertension in 5.7%) and sunitinib in 21.6% (28). Elevated BPs are dose dependent and can be seen as early as 24 hours of starting therapy and are reversible on stopping. The half-life of bevacizumab is 20 days, so patients need to have their BP monitored for a minimum of 3 months after discontinuation of therapy. Actual changes in BP for bevacizumab are quoted at around 10/6 mmHg in the first 60 days (median) and for sorafenib changes in 24-hour BP monitoring of 8.2/6.5 mmHg have been described (36,37).

Bevacizumab leads to a higher incidence of hypertension when used in combination with 5-fluorouracil (38,39). Hypertension can also occur with ocular administration of bevacizumab (40). Such is the risk that the Joint National Commission advocates that a change in the

diastolic BP from baseline of greater than 20 mmHg is an indication for treatment regardless of whether the recommended levels where treatment is indicated are reached.

Chemotherapeutic agents cannot be discontinued or reduced in the majority of cases, but hypertension treatment needs to be managed as a priority, as comorbidities are independent contributors for poor prognosis in cancer patients. Any antihypertensive agent can be used for treatment but dihydropyridine CCBs are effective especially for the short-acting drugs. Verapamil, diltiazem and nifedipine should be avoided, as they can provoke VEGF secretion (31). Antihypertensive medication may be less effective with bevacizumab and rarely discontinuation may be necessary for uncontrolled hypertension. Good control of pre-existing hypertension may also help alleviate any further worsening of hypertension and the potential for associated cardiotoxicity.

The immunosuppressant ciclosporin can result in nephrotoxicity and hypertension. Hypertension develops in 50–80% of patients who receive ciclosporin after kidney, heart or liver transplantation (41). One year after renal transplantation, the incidence is 32.7–81.6% (42,43). Loss of nocturnal dipping in ambulatory BP is seen along with systolic and diastolic hypertension (43). Hypertension may also result from increased SNS activity, increased renal proximal tubular reabsorption of sodium, changes in the production of vasodilating prostaglandins, stimulating the RAAS axis and through direct effects (41). Risk factors for hypertension with ciclosporin include pre-existing hypertension, concurrent corticosteroid therapy and poor renal function (42). Hypertensive crises with encephalopathy induced by ciclosporin have also been described (42). The diastolic BP correlates with the trough levels of ciclosporin, suggesting some dose response, and hypertension may improve with dose reduction. Discontinuation may not always lead to a reduction in BP levels to baseline. Preferred antihypertensive medications include CCBs but avoid non-dihydropyridine CCBs as they can result in a paradoxical increase in ciclosporin levels through cytochrome p450 inhibition. An alternative calcineurin inhibitor is tacrolimus, which has less hypertensive tendency but can lead to salt and fluid retention. Other immunosuppressants such as rapamycin and mycophenolate mofetil do not result in hypertension.

## RECOMBINANT HUMAN ERYTHROPOIETIN

One in three recombinant human erythropoietin (EPO) users will develop hypertension, which can present as new-onset hypertension, worsening of pre-existing hypertension or in the form of a hypertensive crises (44). Risk factors include pre-existing hypertension and a family history of hypertension. This is a dose-dependent effect and can become apparent after 2–16 weeks (45). The pathophysiology is complex and not just related to increased blood viscosity. Increased production of endogenous pressors, reduced responsiveness to vasodilators and arterial modelling have all been described (44). EPO can also increase cytosolic calcium concentrations, leading to reduced nitric oxide-mediated vasodilation (44). Hypertension induced by EPO can be treated with a single antihypertensive agent in 42% of patients (46). General management consists of

treatment with diuretics, and dialysis may need to be considered. Venesection can also help for those patients with more resistant hypertension.

### ANTIHYPERTENSIVE MEDICATION INCLUDING ABRUPT WITHDRAWAL OF MEDICATION

$\alpha$ -Methyldopa can lead to a transient increase in BP before BP decreases. Abrupt withdrawal of clonidine,  $\alpha$ -methyldopa,  $\beta$ -blockers, minoxidil, nifedipine and guanethidine have all been associated with rebound hypertension (45,47,48). Clonidine withdrawal leads to rapid continuation of catecholamine production which had been suppressed, leading to a life-threatening illness (48). The effects are worse the higher the dose.  $\beta$ -blockers provoke receptor upregulation, and sudden withdrawal can result in profound hypertension, and so gradual dose tapering is advised (47). The withdrawal effects may be less with selective  $\beta$ -1 blockers and longer-acting versions (47). Extra care is needed in patients who are on both  $\beta$ -blockers and clonidine, as sudden clonidine withdrawal leads to an even greater rebound hypertension, as there will be unopposed  $\alpha$ -receptor stimulation and lack of  $\beta$ -2 adrenoceptor-mediated vasodilatation (48). Monoamine oxidase inhibitors can lead to hypertensive crises if foods or beverages containing tyramine are consumed concomitantly. Hypertension can also be the result of withdrawal from benzodiazepines and opiates.

### AMPHETAMINES

Amphetamines are used to treat attention-deficit/hyperactivity disorder (ADHD) in children and adolescents. They lead to increases in BP similar to those seen with cocaine. In children, increases in only the diastolic BP of 3.9 mmHg have been reported, whereas in adults increases in both systolic and diastolic BP have been seen (3.5 and 2.4 mmHg, respectively) (49). The European Child and Adolescent Psychiatry Guidelines recommend using lowest possible doses, use of drug holidays and also consideration of behavioural therapies as an alternative to medication. Guanfacine, an  $\alpha$ -2 agonist, is also used in ADHD, and may help counter the BP elevation.

### ANAESTHETICS

Many anaesthetic agents such as propofol are potent hypotensive agents largely due to profound arterial and venous dilatation. However, a number of anaesthetic drugs can lead to temporary effects on BP regulation, leading to hypertension. Ketamine increases heart rate, systolic BP and total peripheral resistance. It also leads to increased pulmonary artery pressure and pulmonary vascular resistance (50). Desflurane also elevates heart rate and BP. BP can also be elevated by drugs if there is an underlying pheochromocytoma. This has been seen with fentanyl, opiates, neuromuscular relaxants and glucagon (51,52). Dexmedetomidine has antianxiety, sedative and analgesic

effects making it useful in anaesthesia. It acts on central  $\alpha$ 2-adrenergic receptors and leads to elevated BP at high doses and reduced BP at low doses.

### ANTI-HUMAN IMMUNODEFICIENCY VIRUS TREATMENTS

Highly active antiretroviral therapy (HAART) can elevate BP after it has been taken for over 6 months, and incidence levels of 26.1% have been reported (53–55). Risk factors for developing hypertension include increasing age, higher systolic BP pretreatment, higher cholesterol levels pretreatment and low CD4 count at diagnosis (56). Systolic BP is more affected than diastolic BP but levels for both have risen by as much as 10 mmHg (53,54). The combination of lopinavir and ritonavir seems to be particularly prone to elevating BP (57).

### ANTIDEPRESSANTS

Tricyclic antidepressants (TADs), fluoxetine and serotonin-norepinephrine reuptake inhibitors lead to elevated BP through sympathomimetic and noradrenergic mediated effects (58). TADs increase both systolic and diastolic BP by 6 mmHg (59). Venlafaxine leads to dose-dependent increases in BP which resolves on discontinuation, male patients and the elderly being more susceptible (60). Monoamine oxidase inhibitors including tranylcypromine and moclobemide also elevate BP, with the former being more troublesome; these effects are more marked if they are given concomitantly with other sympathomimetics.

### SYMPATHOMIMETICS

Decongestants are commonly available in a variety of formulations over the counter. They stimulate  $\alpha$ -1 adrenergic receptors resulting in vasoconstriction. The bioavailability of phenylephrine is increased by acetaminophen, which leads to enhanced BP elevation (61). These are dose-dependent effects and increases in diastolic BP, systolic BP and heart rate are observed (61). The preparation type appears to be important, as sustained-release preparations have less effect on increasing BP than shorter-acting versions. There may also be tolerance to short-release preparations (62). On a practical level, the evidence suggests that short courses of decongestants used sparsely may not lead to long-term adverse effects. One exception here is patients with baroreflex failure, in which any sympathomimetic can lead to severe elevations in BP leading to a stroke (63). Ocular administration of sympathomimetic amines has also led to systemic hypertension. Appetite suppressants such as sibutramine, a serotonin-norepinephrine receptor inhibitor, causes  $\alpha$ -adrenergic agonism through postsynaptic receptor binding and facilitates norepinephrine release from neuronal storage sites, resulting in elevation of BP. Mirabegron is licensed for the treatment of an overactive bladder and leads to bladder relaxation through stimulation of  $\beta$ -3 adrenergic receptors situated in the detrusor muscle. A common adverse effect is hypertension through agonism of the  $\beta$ -3 adrenergic receptors in the

cardiovascular system. This has led to its use being contraindicated in patients with severe uncontrolled hypertension. Patients who are on mirabegron should have their blood pressure checked before starting and at regular intervals after.

## HERBAL SUPPLEMENTS

Herbal supplements are available readily and many do not have robust data regarding their safety and/or efficacy. Supplements associated with elevations in BP include ephedra (including ma-huang), St John's Wort, yohimbine, ginseng and bitter orange (64). Ephedra consists of various alkaloid and nonalkaloid components such as ephedrine and pseudoephedrine. Ephedra has been associated with hypertensive emergencies and deaths, and some supplements contain caffeine (65,66). Ephedra-containing ephedrine alkaloids have now been banned in a number of countries due to these adverse effects. The underlying mechanisms for many herbal supplements remain unknown, but ephedra and bitter orange are  $\alpha$ -1 agonists and elevate BP by up to 10 mmHg (67). Ginger root has been shown to have a pressor effect in animals, and a case report has suggested it can elevate BP in humans (64). A drug interaction between diuretics and ginkgo can also lead to hypertension (68). Vitamin A and its derivatives and iron in overdose can all elevate BP.

## ILLICIT DRUGS

Cocaine leads to acute hypertension through adrenergic overactivity. It inhibits the peripheral reuptake of norepinephrine, resulting in synaptic neurotransmitter accumulation leading to excessive stimulation of adrenergic receptors. The result is BP elevation through vasoconstriction, amongst other SNS effects. Regular users have higher baseline systolic BP. Nevertheless, it is the acute users who run the risk of sudden, dangerously elevated levels of BP. This is seen within 15 minutes of use and is more enhanced when cocaine is taken intranasally (69). Furthermore, presence of pre-existing hypertension can result in much higher BP elevations. Management usually consists of benzodiazepines and sublingual nitroglycerin. More severe cases are likely to require intravenous therapy, and the agents of choice are nitroglycerin, nitroprusside, or phentolamine. It is important to avoid  $\beta$ -blockers, as these can lead to unopposed  $\alpha$ -adrenergic receptor stimulation, which can exacerbate the situation.

## ALCOHOL

Heavy drinkers have a higher prevalence of chronic hypertension (70–72). Excessive alcohol intake also results in resistance to antihypertensive treatments. The effect appears to be dose dependent. The prevalence of alcohol-induced hypertension varies, and rates of 7–11% have been reported (70,71). Proposed mechanisms include impaired baroreflex activity, increased sympathomimetic activity, cortisol hypersecretion, activation of RAAS and abnormal vasoconstriction through effects on calcium channels

(73–75). When alcohol is taken with the anti-abuse drug disulfiram, the resulting reaction also elevates BP.

## CAFFEINE

Acute ingestion of 200–300 mg caffeine in caffeine-naïve subjects leads to increases in systolic and diastolic BPs of 8.1 and 5.7 mmHg, respectively (76). Elevations of 10 mmHg after 2–3 cups have been reported, and an average increase of 4–5/3 mmHg (77). These effects are seen 1 hour after ingestion and peak at 3 hours. The mechanism includes increased sympathetic activity, raised catecholamine levels and antagonism of endogenous adenosine (76). With chronic use, the BP changes are less apparent.

## MISCELLANEOUS DRUGS AND TOXINS

L-dopa and yohimbine lead to sympathomimetic activity through presynaptic changes, which leads to hypertension (78). Physostigmine when given orally also activates central sympathetic activity, leading to elevated BP. The disease modifying antirheumatic drug leflunomide results in increased BP in up to 5–10% of users (79). Systemic antifungals such as ketoconazole lead to hypertension through mineralocorticoid effects (80). Growth hormone and thyroid hormones can increase BP by both metabolic and cardiac effects. There is associated tachycardia, and vascular remodelling occurs with prolonged use. Thyrotropin-releasing hormone is also associated with an acute increase in BP. Midodrine, a prodrug of the sympathomimetic agent desglymidodrine, acts on peripheral- $\alpha$  receptors and leads to elevations in BP. Atypical antipsychotics – for example clozapine and olanzapine – are also associated with hypertension, but this may be the result of their effects on weight gain and precipitation of the metabolic syndrome (81). Metoclopramide and prochlorperazine can transiently increase BP levels when they follow cisplatin therapy. Metoclopramide can also increase BP when there is an occult pheochromocytoma. Lead, thallium, cadmium and arsenic can all lead to raised BP (82–84). Venom from scorpions and the black widow spider leads to massive catecholamine discharge, which elevates BP (85). Organophosphates bind to nicotinic receptors, leading to elevated BPs (86).

## CONCLUSION

There is a broad spectrum of drugs that can elevate BP in a manner which can be transient or persistent. The underlying mechanisms are widespread. In many cases, discontinuation of the drug or dose reduction will lead to resolution of hypertension. In some cases, this is not possible and antihypertensive therapy is needed. Drug-induced hypertension that does not resolve on discontinuation of the medication raises the risk of longer-term cardiovascular illness. Given the potential for both short- and long-term adverse outcomes, drug-induced hypertension merits greater awareness amongst clinicians and should be actively sought for and carefully managed in affected patients.



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## REFERENCES

- Whitworth J. Mechanisms of glucocorticoid-induced hypertension. *Kidney Int* 1987; 31: 1213–1224.
- Brookes L. National Health and Nutrient Examination Survey (NHANES) data on hypertension. In: *American Society of Hypertension 18th Annual Scientific Session*. 2003.
- Whitworth JA, Brown MA, Kelly JJ, Williamson PM. Mechanisms of cortisol-induced hypertension in humans. *Steroids* 1995; 60: 76–80.
- Pirpiris M, Sudhir K, Yeung S et al. Pressor responsiveness in corticosteroid-induced hypertension in humans. *Hypertension* 1992; 19(6 Pt 1): 567–574.
- Pope JE, Andersen JJ, Felsen DT. A meta-analysis of the effects of non-steroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med* 1993; 153: 477–484.
- Johnson AG, Nguyen TV, Day RO. Do non-steroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Ann Intern Med* 1994; 121: 289–300.
- Johnson AG. NSAIDs and increased blood pressure. What is the clinical significance? *Drug Saf* 1997; 17(5): 277–289.
- Armstrong EP. The impact of non-steroidal anti-inflammatory drugs on blood pressure in patients treated with different anti-hypertensive drugs. *Clin Ther* 2003; 25(1): 1–18.
- Bavry AA, Khaliq A, Gong Y et al. Harmful effects of NSAIDs among patients with hypertension and coronary artery disease. *Am J Med* 2011; 124(7): 614–620.
- Palmer R, Weiss R, Zusman RM et al. Effects of nabumetone, celecoxib, and ibuprofen on blood pressure control in hypertensive patients on angiotensin converting enzyme inhibitors. *Am J Hypertens* 2003; 16: 135–139.
- Chobanian AV, Bakris GL, Black HR et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003; 42(6): 1206–1252.
- Aw TJ, Haas SJ, Liew D, Krum H. Meta-analysis of cyclooxygenase-2 inhibitors and their effects on blood pressure. *Arch Intern Med* 2005; 165(5): 490–496.
- Sowers JR, White WB, Pitt B et al. The effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patient with hypertension, osteoarthritis, and type 2 diabetes mellitus. *Arch Intern Med* 2005; 165(2): 161–168.
- Solomon SD, Pfeffer MA, McMurray JJ et al. Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. *Circulation* 2006; 114(10): 1028–1035.
- White WB. Cardiovascular effects of the cyclooxygenase inhibitors. *Hypertension* 2007; 49(3): 408–418.
- Sudano I, Flammer AJ, Periat D et al. Acetaminophen increases blood pressure in patients with coronary artery disease. *Circulation* 2010; 122(18): 1789–1796.
- Forman JP, Rimm EB, Curhan GC. Frequency of analgesic use and risk of hypertension among men. *Arch Intern Med* 2007; 167(4): 394–399.
- Chasen-Taber L, Willett WC, Manson JE et al. Prospective study of oral contraceptives and hypertension among women in the United States. *Circulation* 1996; 94(3): 483–489.
- Narkiewicz K, Graniero GR, D'Este D et al. Ambulatory blood pressure in mild hypertensive women taking oral contraceptives. A case-control study. *Am J Hypertens* 1995; 8: 249–253.
- Mandel FP, Geola FL, Lu JK et al. Biologic effects of various doses of ethinyl estradiol in postmenopausal women. *Obstet Gynecol* 1982; 59: 673–679.
- Hussain SF. Progestogen-only pills and high blood pressure: Is there an association? A literature review. *Contraception* 2004; 69(2): 75–83.
- Francomano D, Lenzi A, Aversa A. Effects of five-year treatment with testosterone undecanoate on metabolic and hormonal parameters in ageing men with metabolic syndrome. *Int J Endocrinol* 2014; 37(4): 401–411.
- Rosca AE, Stoian I, Badiu C et al. Impact of chronic administration of anabolic androgenic steroids and taurine on blood pressure in rats. *Braz J Med Biol Res* 2016; 49(6): e5116.
- Rasmussen JJ, Schou M, Madsen PL et al. Increased blood pressure and aortic stiffness among abusers of anabolic androgenic steroids: Potential effects of suppressed natriuretic peptides in plasma? *J Hypertens* 2017; 36(2): 277–e5285.
- Piccirillo JF, Tierney RM, Costas I et al. Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA* 2004; 291(20): 2441–2447.
- Handler J. Hypertension complicating cancer chemotherapy. *J Clin Hypertens* 2006; 8(7): 526–529.
- Jaffe M, Kletzel N. Systemic hypertension: Complication of intra-arterial cis-diammine dichloroplatinum (II) infusion. *Cancer* 1981; 47(2): 245–247.
- Wu S, Chen JJ, Kudelka A et al. Incidence and risk of hypertension with sorafenib in patients with cancer: A systematic review and meta-analysis. *Lancet Oncol* 2008; 9(2): 117–123.
- Hood JD, Meininger CJ, Ziche M, Granger HJ. VEGF upregulates eNOS message, protein, and NO production in human endothelial cells. *Am J Physiol* 1998; 274(3 Pt 2): H1395–H1401.
- Kappers MH, van Esch JH, Sluiter W et al. Hypertension induced by the tyrosine kinase inhibitor sunitinib is associated with increased circulating endothelin-1 levels. *Hypertension* 2010; 56(4): 675–681.
- Izzedine H, Ederhy S, Goldwasser F et al. Management of hypertension in angiogenesis inhibitor-treated patients. *Ann Oncol* 2009; 20(5): 807–815.
- Escudier B, Eisen T, Stadler WM et al. Sorafenib in advanced clear cell renal-cell carcinoma. *N Engl J Med* 2007; 356(2): 125–134.
- Kozloff M, Yood MU, Berlin J et al. Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: The BRiTE observational cohort study. *Oncologist* 2009; 14(9): 862–870.
- Levy CF, Oo KZ, Fireman F et al. Reversible posterior leukoencephalopathy syndrome in a child treated with bevacizumab. *Paediatr Blood Cancer* 2009; 52(5): 669–671.
- Yang JC, Haworth L, Sherry RM et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003; 349: 427–434.
- Hurwitz HJ, Douglas PS, Middleton JP et al. Analysis of early hypertension and clinical outcome with Bevacizumab: Results from seven phase III studies. *Oncologist* 2013; 18(3): 1–2.
- Maitland ML, Kasza KE, Karrison T et al. Ambulatory monitoring detects sorafenib-induced blood pressure elevations on the first day of treatment. *Clin Cancer Res* 2009; 15(19): 6250–6257.
- Rosiak J, Sadowski L. Hypertension associated with bevacizumab. *Clin J Oncol Nurse* 2005; 9: 407–411.
- Gordon MS, Cunningham D. Managing patients treated with bevacizumab combination therapy. *Oncology* 2005; 69(Suppl 3): 25–33.
- Heybani A, Kymes S, Schlieff S, Apte R. Vascular events in patients with age-related macular degeneration treated with intraocular bevacizumab. *Retina* 2009; 29(10): 1404–1408.
- Morales JM, Andres A, Rengel M, Rodicio JL. Influence of cyclosporin, tacrolimus and rapamycin on renal function and arterial hypertension after renal transplantation. *Nephrol Dial Transplant* 2001; 16(Suppl. 1): 121–124.
- Ponticelli C, Montagnino G, Aroldi A et al. Hypertension after renal transplantation. *Am J Kidney Dis* 1993; 21: 73–78.
- Snanoudj R, Kriaa F, Arzouk N. Single-center experience with cyclosporine therapy for kidney transplantation: Analysis of a twenty-year period in 1200 patients. *Transplant Proc* 2004; 36(2 Suppl): 83S–88S.
- Novak BL, Force RW, Mumford BT, Solbrig RM. Erythropoietin-induced hypertensive urgency in a patient with chronic renal insufficiency: Case report and review of the literature. *Pharmacotherapy* 2003; 23(2): 265–269.
- Grossman E, Messerli FH. High blood pressure. A side effect of drugs, poisons, and food. *Arch Intern Med* 1995; 155(5): 450–460.
- Eschbach JW, Aquilino T, Haley NR. The long-term effects of human recombinant erythropoietin on the cardiovascular system. *Clin Nephrol* 1992; 38(Suppl 1): S98–S103.
- Krukemeyer JJ, Boudoulas H, Binkley PF, Lima JJ. Comparison of hypersensitivity to adrenergic stimulation after abrupt withdrawal of propranolol and nadolol: Influence of half-life differences. *Am Heart J* 1990; 120: 572–579.
- Lilja M, Jounela AJ, Juustila HJ, Paalzow L. Abrupt and gradual change from clonidine to beta blockers in hypertension. *Acta Med Scand* 1982; 211: 375–380.

49. Buitelaar JK, Ramos-Quiroga JA, Casa M et al. Safety and tolerability of flexible dosages of prolonged-release OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. *Neuropsychiatr Dis Treat* 2009; 5: 457–466.
50. Reich DL, Silvey G. Ketamine: An update on the first twenty-five years of clinical experience. *Can J Anaesth* 1989; 36: 186–197.
51. Watson DL, Bhatia RK, Norman GS et al. Bromocriptine mesylate for lactation suppression: A risk for postpartum hypertension? *Obstet Gynecol* 1989; 74: 821–822.
52. Bakht FR, Kirshon B, Baker T, Cotton DB. Postpartum cardiovascular complications after bromocriptine and cocaine use. *Am J Obstet Gynecol* 1990; 162: 1065–1066.
53. Grandominico JM, Fichtenbaum CJ. Short-term effect of HAART on blood pressure in HIV-infected individuals. *HIV Clin Trials* 2008; 9(1): 52–60.
54. Glass TR, Ungsedhapand C, Wolbers M et al. Prevalence of risk factors for cardiovascular disease in HIV-infected patients over time: The Swiss HIV Cohort Study. *HIV Med* 2006; 7(6): 404–410.
55. Cattelan AM, Trevenzoli M, Naso A et al. Severe hypertension and renal atrophy associated with indinavir. *Clin Infect Dis* 2000; 30(3): 619–621.
56. Baekken M, Os I, Sandvik L, Oektedalen O. Hypertension in an urban HIV-positive population compared with the general population: Influence of combination antiretroviral therapy. *J Hypertens* 2008; 26(11): 2126–2133.
57. Crane HM, Van Rompaey SE, Kitahata MM. Antiretroviral medications associated with elevated blood pressure among patients receiving highly active antiretroviral therapy. *AIDS* 2006; 20(7): 1019–1026.
58. Amsterdam JD, Garcia-Espana F, Fawcett J et al. Blood pressure changes during short-term fluoxetine treatment. *J Clin Psychopharmacol* 1999; 19: 9–14.
59. Licht CM, de Geus EJ, Seldenrijk A et al. Depression is associated with decreased blood pressure, but antidepressant use increases the risk for hypertension. *Hypertension* 2009; 53: 631–638.
60. Thase ME. Effects of venlafaxine on blood pressure: A meta-analysis of original data from 3744 depressed patients. *J Clin Psychiatry* 1998; 59(10): 502–508.
61. Atkinson HC, Stanescu I, Salem II et al. Increased bioavailability of phenylephrine by co-administration of acetaminophen: Results of four open-label, crossover pharmacokinetic trials in healthy volunteers. *Eur J Clin Pharmacol* 2015; 71: 151–158.
62. Salerno SM, Jackson JL, Berbano EP. Effect of oral pseudoephedrine on blood pressure and heart rate: A meta-analysis. *Arch Intern Med* 2005; 165: 1686–1694.
63. Ketch T. Four faces of Baroreflex failure: Hypertensive crisis, volatile hypertension, orthostatic tachycardia, and malignant vagotonia. *Circulation* 2002; 105(21): 2518–2523.
64. Newell CA, Anderson LA, Philipson JD. *Herbal Medicines: A Guide for Healthcare Professionals*. Pharmaceutical Press, London; 1996.
65. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 2000; 343(25): 1833–1838.
66. McBride BF, Karapanos AK, Krudysz A. Electrocardiographic and haemodynamic effects of a multicomponent dietary supplement containing ephedra and caffeine: A randomized controlled trial. *JAMA* 2004; 291: 216–221.
67. Haller CA, Benowitz NL, Jacob 3rd P. Haemodynamic effects of ephedra-free weight-loss supplements in humans. *Am J Med* 2005; 118: 998–1003.
68. Izzo AA, Di Carlo G, Borrelli F, Ernst E. Cardiovascular pharmacotherapy and herbal medicines: The risk of drug interaction. *Int J Cardiol* 2005; 98(1): 1–14.
69. Tuncel M, Wang Z, Arbique D et al. Mechanisms of the blood pressure-raising effect of cocaine in humans. *Circulation* 2002; 105: 1054–1059.
70. Klatsky AL, Friedman GD, Siegalaub AB, Gerard MJ. Alcohol consumption and blood pressure Kaiser-Permanente Multiphasic Health Examination data. *N Engl J Med* 1977; 296(21): 1194–1200.
71. MacMahon SW, Blacket RB, Macdonald GJ, Hall W. Obesity, alcohol consumption and blood pressure in Australian men and women. The National Heart Foundation of Australia Risk Factor Prevalence Study. *J Hypertens* 1984; 2(1): 85–91.
72. Yoshita K, Miura K, Morikawa Y et al. Relationship of alcohol consumption to 7-year blood pressure change in Japanese men. *J Hypertens* 2005; 23(8): 1485–1490.
73. Grassi GM, Somers VK, Renk WK. Effects of alcohol intake on blood pressure and sympathetic nerve activity in normotensive humans: A preliminary report. *J Hypertens Suppl* 1989; 7: S20–S21.
74. Arkwright PD, Beilin LJ, Vandongen R et al. Plasma calcium and cortisol as predisposing factors to alcohol related blood pressure elevation. *J Hypertens* 1984; 2: 387–392.
75. Coca A, Aguilera MT, De la Sierra A, Urbano-Marquez A. Chronic alcohol intake induces reversible disturbances on cellular NA metabolism in humans: Its relationship with changes in blood pressure. *Alcohol Clin Exp Res* 1992; 16: 714–720.
76. Savoca MR, MacKey ML, Evans CD et al. Association of ambulatory blood pressure and dietary caffeine in adolescents. *Am J Hypertens* 2005; 18(1): 116–120.
77. Cohen DL, Townsend RR. Does consumption of high-caffeine energy drinks affect blood pressure? *J Clin Hypertens (Greenwich)* 2006; 8(10): 744–745.
78. Goldstein DS, Eisenhofer G, Garty M et al. Pharmacologic and tracer methods to study sympathetic function in primary hypertension. *Clin Exp Hypertens* 1989; 11(Suppl 1): 173–189.
79. Scott DL, Smolen JS, Kalden JR et al. Treatment of active rheumatoid arthritis with leflunomide: Two year follow up of a double blind, placebo controlled trial versus sulfasalazine. *Ann Rheum Dis* 2001; 60: 913–923.
80. Asbo K, De Coster R. Hypertension during high-dose ketoconazole treatment: A probable mineralocorticoid effect. *Lancet* 1987; 2: 637–638.
81. Freyburg Z, Aslanoglou D, Sha R, Ballon JS. Intrinsic and antipsychotic drug-induced metabolic dysfunction in schizophrenia. *Front Neurosci* 2017; 11: 432.
82. Martin D, Glass TA, Bandeen-Roche K et al. Association of blood lead with blood pressure and hypertension in a community sample of older adults. *Am J Epidemiol* 2006; 163: 467–478.
83. Wainwright AP, Kox WJ, House IM et al. Clinical features and therapy of acute thallium poisoning. *Q J Med* 1988; 69: 939–944.
84. Chen CJ, Hseuh YM, Lai MS et al. Increased prevalence of hypertension and long-term arsenic exposure. *Hypertension* 1995; 25: 53–60.
85. Sofer S, Shalev H, Weizman Z et al. Acute pancreatitis in children following envenomation by the yellow scorpion *Leiurus quinquestriatus*. *Toxicon* 1991; 29: 125–128.
86. Saadeh AM, Farsakh NA, al-Ali MK. Cardiac manifestations of acute carbamate and organophosphate poisoning. *Heart* 1997; 77: 461–464.
87. Lichtenstein K, Balasubramanyam A, Sekhar R, Freedland E. HIV-associated adipose redistribution syndrome (HARS): Etiology and pathophysiological mechanisms. *AIDS Res Ther* 2007; 4(14).
88. Bartness TJ, Song CK. Sympathetic and sensory innervation of white adipose tissue. *J Lipid Res* 2007; 48: 1655–1672.
89. Boccara F, Auclair M, Cohen A et al. HIV protease inhibitors activate the adipocyte renin angiotensin system. *Antivir Ther* 2010; 15(3): 363–375.
90. Liebe T, Li S, Lord A et al. Factors influencing the cardiovascular response to subanesthetic ketamine: A randomized, placebo-controlled trial. *Int J Neuropsychopharmacol* 2017; 20(11): 909–918.

# HYPERTENSION IN PATIENTS WITH ADVANCED CHRONIC KIDNEY DISEASE

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## INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem affecting more than 10% of adults in developed societies, while its incidence rate is around 0.2% in the general population (1,2). The prevalence of end-stage renal disease (ESRD) is small, around 0.2 of the general population, but represents a major problem of public health (3). The most common comorbidity accompanying CKD is hypertension, which appears in approximately 80% of all patients with renal dysfunction, whereas its prevalence in general population is remarkably lower (4,5). It has been found that with progression of CKD from stage 1 towards stages 4–5, a parallel 15–30% increase occurs in the prevalence of hypertension, based on office blood pressure (BP) measurements (4). Population studies have shown around 70–80% of patients with stage 1 CKD to be hypertensive, while in stages 4 and 5 this rate increases to more than 95% (4). Herein we discuss the epidemiology, pathogenesis and management of hypertension in patients with advanced CKD (i.e. at stages 3b, 4 and 5) and with ESRD on maintenance dialysis.

## HYPERTENSION IN PATIENTS WITH ADVANCED CKD

### EPIDEMIOLOGY

Elevated BP is a major risk factor for CKD, whereas kidney injury can cause hypertension (6–9). In the Multiple Risk Factor Intervention Trial (MRFIT), which included 332,544 middle-aged men, BP was a strong predictor for development of ESRD (10). A previous study in 2825 non-diabetic, hypertensive adults found that almost 25% had occult CKD (defined as estimated glomerular filtration rate [eGFR]  $\leq 60$  mL/min/1.73 m<sup>2</sup> and/or urine albumin-to-creatinine ratio [ACR]  $\geq 30$  mg/g among patients with eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>) (11). The prevalence of hypertension in patients with CKD has been evaluated in a cross-sectional analysis of 10,813 CKD patients participating in the Kidney Early Evaluation Program (KEEP) in the United

States; hypertension (defined as BP  $\geq 130/80$  mmHg or use of antihypertensive drugs) was detected in 86.2% of the overall study cohort. The prevalence of hypertension exhibited a stepwise increase with advancing stages of CKD, increasing to 95.5% (or 91% with the use of 140/90 threshold) in participants with stages 4 and 5 CKD (4). Another study in patients with advanced CKD before dialysis followed in a low-clearance clinic (mean eGFR 14.5 mL/min/1.73 m<sup>2</sup>) showed the prevalence of hypertension to be 95% (12), indicating that almost all CKD patients just before the initiation of renal replacement therapy are hypertensive. Of note, a seminal study using ambulatory BP monitoring (ABPM) to examine hypertension in CKD showed the rates of white-coat and masked hypertension to be around 30% and 7%, respectively (13).

### PATHOGENESIS

The role of kidneys in the pathogenesis of essential hypertension is well established (14). In patients with reduced renal mass, several of the mechanisms that originate from the kidney and promote hypertension are exaggerated (8,15), such as further reduction of the kidney's ability to handle dietary sodium leading to increased sodium sensitivity, as well as sodium and water retention (16), activation of the renin–angiotensin system (RAS) and the sympathetic nervous system (SNS), impaired nitric oxide (NO) synthesis and endothelium-mediated vasodilatation and others (Table 57.1). Complications unique to CKD, such as secondary hyperparathyroidism and increased calcium-phosphate products leading to elevated arterial stiffness, or increased prevalence of sleep apnoea, as well as use of specific drugs such erythropoietin, steroids or calcineurin inhibitors may also be involved.

## TREATMENT OF HYPERTENSION IN PATIENTS WITH ADVANCED CKD

### BP TARGETS FOR PATIENTS WITH CKD

Until the recent publication of the 2017 American College of Cardiology (ACC) - American Heart Association (AHA)

**Table 57.1** Main mechanisms for blood pressure elevation in patients with CKD

|                                                                                 |
|---------------------------------------------------------------------------------|
| Pre-existing essential hypertension                                             |
| Sodium and water overload                                                       |
| Renin–angiotensin–aldosterone system stimulation                                |
| Increased sympathetic activity                                                  |
| Endogenous digitalis-like factors                                               |
| Alterations in endothelium-derived factors (nitric oxide/endothelin)            |
| Parathyroid hormone secretion/increased arterial stiffness                      |
| Calcification of arterial tree leading to increased arterial stiffness          |
| Renal artery disease                                                            |
| Chronic allograft dysfunction                                                   |
| Cadaver allografts, especially from a donor with family history of hypertension |
| Drug use: Erythropoietin-stimulating agents, steroids, cyclosporin, tacrolimus  |

High BP Clinical Practice Guideline (17), the BP level of 140/90 mmHg for diagnosis and treatment of hypertension in the general hypertensive population met little criticism over the past 30 years. However, the optimal level to which BP should be reduced in individuals with CKD (or diabetes) has been a matter of considerable debate (18,19). Previous observational studies suggested a strong association between high BP and the risk for renal function decline or ESRD, while in various clinical trials patients with BP below conventional thresholds showed better preservation of renal function (6,8). Thus, previous hypertension guidelines recommended a BP target of <130/80 mmHg for all CKD patients (and possibly <125/75 for those with proteinuria >1 g/day) (20,21), although evidence from trials with hard renal outcomes (i.e. incidence of ESRD) randomizing patients to different BP targets was limited (18). In more recent years, long-term cohort data of renal trials supported a low BP goal for patients with proteinuria, whereas cardiovascular trials questioned the beneficial effects of low BP for diabetic patients, leading to modification of the recommended BP targets in some cases (7,18). Herein, we discuss briefly the relevant evidence.

In patients with nondiabetic CKD two clinical trials with hard renal endpoints have evaluated different BP targets: the Modification of Diet in Renal Disease (MDRD) study included two substudies in CKD [585 patients in study A (GFR 25–55 mL/min/1.73 m<sup>2</sup>) and 255 in study B (GFR 13–24 mL/min/1.73 m<sup>2</sup>)] with primary outcome the rate of change in GFR (GFR slope), and mean follow-up 2.2 years (22). Diabetic patients on insulin were excluded by protocol; thus only 26 patients with diabetic nephropathy participated. In a 2 × 2-factorial design, patients were randomized to different levels of dietary protein and to a usual BP-goal [mean arterial pressure (MAP) <107 mmHg for patients ≤60 years (roughly corresponding to <140/90) and <113 for patients ≥61 years] or a low goal [MAP <92 mmHg for patients ≤60 years (corresponding to

<125/75) and <98 for patients ≥61 years]. The projected GFR decline in 3 years (10.7 vs. 11.5 mL/min/1.73 m<sup>2</sup>), and the risk of ESRD and death (hazard ratio [HR] 0.85, 95% CI: 0.60–1.22 for low BP arm) were not significantly different between groups (22). However, analyses of patients by baseline proteinuria showed that those with baseline proteinuria >1 g/day in the low target group had a significant decrease in proteinuria and a significantly slower reduction in GFR compared to patients assigned to the usual target group (23). In patient-level meta-analysis of trials on antihypertensive treatment with or without angiotensin-converting enzyme inhibitors (ACEIs) in predominantly nondiabetic CKD patients, a systolic BP of 110–129 mmHg was associated with the lowest risk of kidney disease progression in patients with urine protein excretion (UAE) >1000 mg/day (1 g/day) (24). A subsequent analysis examined long-term outcomes adding the trial phase of MDRD (1989–1993) and a cohort period (1993–2000) during which no specific target BP was recommended (25). During a median follow-up of 10.7 years low target BP was associated with reduced risk for ESRD (HR 0.68; 95% CI: 0.57–0.82) and the composite of ESRD or death (HR 0.77; 95% CI: 0.65–0.91), compared with usual target BP. Again, in subgroup analyses, the benefits from low target BP for ESRD and the composite endpoint became significant for proteinuria >1 g/day. The *P*-value for interaction of target BP with proteinuria was 0.09 for ESRD and 0.08 for the composite outcome (25).

The African American Study on Kidney Disease (AASK) included 1094 African Americans with hypertensive CKD (GFR, 20–65 mL/min/1.73 m<sup>2</sup>, mean proteinuria 0.6 g/day), randomized to MAP 102–107 or ≤92 mmHg, and to initial treatment with metoprolol, ramipril, or amlodipine in a 3 × 2 factorial design. Results from this study showed that patients randomized to MAP <92 mmHg had no benefit from this intervention in comparison with patients randomized to the usual target (26). Again, a post hoc analysis of this trial showed that baseline proteinuria was the key factor that defined the above results, as the lower BP target did preserve renal function in the small subset of patients with proteinuria >1000 mg/day (1 g/day) (27). After the trial-phase, around 700 subjects were enrolled in an observational phase with a total follow-up 8.8–12.2 years; target BP during the cohort phase was <130/80 mmHg. A recent analysis included the two phases together, showing no significant difference in the risk of the composite outcome of doubling of serum creatinine (SCr), ESRD, or death (HR 0.91; 95% CI: 0.77–1.08 in low-BP group). However, there was a significant interaction with the baseline level of proteinuria (*p* = 0.02); patients with urine protein-to-creatinine ratio (UPCR) >0.22 (both measured in 24-hour collections and expressed in mg/dL), which roughly equals proteinuria of 320 mg/day, had lower risk of the primary outcome with intensive treatment (HR 0.73; 95% CI: 0.58–0.93). In those with UPCR ≤0.22 there was no between-group difference (HR 1.18; 95% CI: 0.93–1.50) (28). Taken together, the findings from MDRD and AASK indicate that a low-BP target is beneficial for long-term renal survival in patients with nondiabetic kidney disease and proteinuria >0.25–0.3 g/day, (equivalent to urine albumin around 0.15 g/day). Thus, a goal BP of <130/80 (i.e. that of AASK cohort study) seems justifiable for proteinuria >0.3 g/day, as we (18,29) (Table 57.2) and the KDIGO Hypertension Guidelines suggested (7).



**Table 57.2** Possible blood pressure targets for patients with kidney disease, according to available evidence from trials with renal and/or cardiovascular primary endpoints

|                        | Protein excretion <0.3 g/day<br>(albumin excretion<br><150 mg/day) | Protein excretion 0.3–1 g/day<br>(albumin excretion<br>150–500 mg/day) | Protein excretion >1 g/day<br>(albumin excretion<br>>500 mg/day)                                      |
|------------------------|--------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| <b>Nondiabetic CKD</b> | <140/90 mmHg                                                       | <130/80 mmHg                                                           | <125/75 mmHg <sup>a</sup>                                                                             |
| <b>Diabetic CKD</b>    | SBP <130–140 mmHg <sup>b</sup><br>DBP <80 mmHg <sup>b</sup>        | <130/80 mmHg <sup>c</sup>                                              | <130/80 mmHg <sup>c</sup><br>(<125/75 mmHg <sup>c</sup> for young<br>patients with heavy proteinuria) |

Source: Modified from Sarafidis PA, Ruilope LM. *Kidney Int* 2014; 85: 536–546. With permission.

<sup>a</sup> As evident from MDRD study B trial phase and MDRD long-term study.

<sup>b</sup> From cardiovascular outcome trials.

<sup>c</sup> Following extrapolation of data from in nondiabetic CKD studies and post hoc or observational analyses in diabetic CKD.

In patients with diabetic CKD, a post hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, which included 1513 patients with type 2 diabetes, hypertension and macroalbuminuria (mean SCr 1.9 mg/dL and median ACR 1237 mg/g) and compared the effects of losartan or placebo on CKD progression, showed that baseline SBP of 140–159 mmHg increased risk for ESRD or death by 38% ( $p = 0.05$ ) compared to SBP <130 mmHg. In a multivariate model, every 10-mmHg rise in baseline SBP increased the risk for ESRD or death by 6.7% ( $p = 0.007$ ), whereas the same rise in DBP decreased the risk by 10.9% ( $p = 0.01$ ) (30). A relevant post hoc analysis of achieved BP and renal outcomes from the Irbesartan Diabetic Nephropathy Trial (IDNT) (which included 1590 patients with type 2 diabetes, hypertension, and proteinuria >900 mg/day, to compare the effects of irbesartan, amlodipine and placebo) showed that SBP >149 mmHg was associated with a 2.2-fold increase in the risk for doubling SCr or ESRD compared with SBP <134 mmHg and follow-up achieved SBP most strongly predicted renal outcomes; moreover, progressive lowering of SBP down to 120 mmHg improved renal and patient survival, but <120 mmHg, all-cause mortality increased (31). Based on evidence like the above and since progression of renal injury is believed to follow the same pathways once proteinuria develops, it has been argued that in patients with proteinuric diabetic nephropathy (particularly >1 g/day), the above BP targets for nondiabetic CKD should apply (6,7,18,29,32).

Recently, the ACC-AHA BP High Blood Pressure Clinical Practice Guideline proposed a level of 130/80 mmHg for the diagnosis and management of hypertension in all individuals, including those with CKD (17). This change is mainly generated from the results of the Systolic Blood Pressure Intervention Trial (SPRINT) in which 9361 hypertensives of increased cardiovascular burden but not diabetes or prior stroke were randomized to intensive (SBP <120 mmHg) or standard treatment (SBP <140 mmHg) based on automated office BP measurements (33). The SPRINT trial was terminated earlier than scheduled, as the rate of the primary composite outcome (MI, acute coronary syndrome not resulting in MI, stroke, acute decompensated HF or death from cardiovascular causes) was significantly lower in the intensive-treatment group compared with the standard-treatment group (HR 0.75; 95% CI: 0.64–0.89;  $p < 0.001$ ). Patients in the intensive-treatment group had a non-significant lower risk of MI

( $p = 0.19$ ) and stroke ( $p = 0.50$ ) but a 38% significantly lower risk of heart failure, 27% lower total mortality and 43% lower cardiovascular mortality. Patients in the intensive-treatment group more frequently developed hypotension (2.4% vs. 1.4%,  $p = 0.001$ ), syncope (2.3% vs. 1.7%,  $p = 0.05$ ), electrolyte abnormalities (3.1% vs. 2.3%,  $p < 0.001$ ), and acute kidney injury (4.1% vs. 2.5%,  $p < 0.001$ ) (33). A recent SPRINT report (34) included the subpopulation of patients with CKD (eGFR 20–60 mL/min/1.73 m<sup>2</sup>) which was considerably high ( $n = 2646$ ). After a median of 3.3 years, the primary outcome was non-significantly lower in the intensive group (HR 0.81; 95% CI: 0.63–1.05), but the intensive group had a lower mortality rate (HR 0.72; 95% CI: 0.53–0.99). The prespecified main kidney outcome, defined as the composite of  $\geq 50\%$  decrease in eGFR from baseline or ESRD, occurred in 15 intensive group and 16 standard group participants (HR 0.90; 95% CI: 0.44–1.83). The overall rate of serious adverse events did not differ between treatment groups. These results must be interpreted with caution, since the SPRINT trial was not powered to study renal outcomes, included few proteinuric patients, and, especially with premature termination of the trial, the number of renal events were small. If anything, the above results rather support the use of the <130/80 mmHg in all individuals with CKD for cardiovascular and mortality benefit, as patients with CKD in the intensive group of SPRINT had lower cardiovascular and all-cause mortality rates and similar rates of the prespecified composite renal outcome.

### USE OF ANTIHYPERTENSIVE AGENTS IN CKD

Following implementation of the lifestyle modifications recommended for all hypertensive individuals (35), with particular attention paid to sodium restriction, as discussed elsewhere (8,36), use of antihypertensive agents in CKD patients should aim to not only effectively lower BP, but also to slow nephropathy progression and reduce the risk of cardiovascular disease. ACEIs and angiotensin receptor-1 blockades (ARBs) are the antihypertensive agents that most consistently have been found in renal outcome trials to reduce the rate of CKD progression, an effect proportionate to proteinuria reduction in proteinuric diabetic and nondiabetic nephropathy (8,37), and are thus suggested as first-line treatment in these individuals (6,7,21,35). Herein, we briefly discuss the evidence from outcome trials on the use of major antihypertensive drug



classes in proteinuric nephropathies. It has to be noted, however, that in hypertensive patients without proteinuria and relatively preserved eGFR (i.e.  $>70\text{--}75\text{ mL/min/1.73 m}^2$ ), there is no evidence from outcome trials on additional renoprotective benefit of RAS blockade. A detailed discussion on the latter field is beyond the scope of this chapter and can be found elsewhere (18).

#### BLOCKERS OF THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

In nondiabetic proteinuric nephropathy, ACEI use was studied in the Ramipril Efficacy In Nephropathy (REIN)-2 study, where patients with mean SCr of 2.4 mg/dL and proteinuria  $>3\text{ g/day}$  were randomized to ramipril or placebo; ramipril showed significant reductions in proteinuria, GFR decline and the risk of SCr doubling or ESRD compared to placebo. The risk of kidney disease progression was still significantly reduced after adjustment for changes in systolic and diastolic BP (38). In the AASK trial analysed above, patients treated with ramipril had a 36% reduction in the composite endpoint of 50% reduction of GFR, ESRD or death compared to amlodipine, and a 22% reduction compared to metoprolol (26). Of particular importance also is the study from Hou et al., who randomized 224 Chinese patients with SCr levels 3.1–5.0 mg/dL ( $274.3\text{--}442.5\text{ }\mu\text{mol/L}$ ) and persistent proteinuria [mean UAE of 1600 mg/day ( $1.6\text{ g/day}$ )] to receive 20 mg of benazepril per day or placebo on top of conventional antihypertensive therapy. Benazepril was associated with a 43% reduction in the risk of the primary endpoint (doubling of SCr, ESRD, or death), a 23% decrease in the rate of decline in renal function and 2.5 times greater reduction in proteinuria compared to placebo after 3.4 years, benefits that were not attributable to better BP control (39). A meta-analysis by the AIPRD Study Group in nondiabetic CKD showed that regimens including an ACEI were associated with a 31% reduction in progression to ESRD and 30% reduction in the combined endpoint in doubling of SCr or progression to ESRD (40).

In patients with diabetes, the use of an ACEI or an ARB is generally recommended for hypertension treatment due to the fact that these agents have positive or neutral effects on glycaemic and lipid control (41). The eminent Collaborative Group Study examined the effects of captopril versus placebo in 409 type 1 diabetic patients with albuminuria  $\geq 0.5\text{ g/day}$  and SCr  $\leq 2.5\text{ mg/dL}$ . After 3 years, treatment with captopril led to 43% reduction in the risk of the primary endpoint of doubling of SCr, 50% reduction in the combined endpoint of death, need for dialysis and transplantation as well as 30% reduction in UAE compared to placebo (42). In the RENAAL study discussed above, losartan-treated patients had a 35% reduction in the urinary albumin-to-creatinine ratio along with a 16% reduction in the primary endpoint of doubling of SCr, progression to ESRD or death. The median rate of decline in estimated clearance was 4.4 and 5.2 mL/min/ $1.73\text{ m}^2$ /per year in the losartan and placebo group, respectively (43). Similarly, in the IDNT study, after a mean follow-up of 2.6 years, proteinuria was decreased by 33% in the irbesartan group versus 6% in the amlodipine group and 10%, in the placebo group. Treatment with irbesartan also resulted in a 20% reduction compared to placebo and 23% reduction compared to amlodipine in the primary composite outcome of doubling of SCr, ESRD or

death. The mean rate of decline of creatinine clearance was  $-5.5$ ,  $-6.8$ , and  $-6.5\text{ mL/min/1.73 m}^2$  per year in the irbesartan, placebo and amlodipine groups, respectively (44). Post hoc analyses of the above two trials investigated the relationship of baseline proteinuria and reductions in proteinuria during follow-up with the outcome. In RENAAL baseline proteinuria had a nearly linear relationship with the risk for the primary outcome. Further, for every 50% reduction in albuminuria in the first 6 months, there was a 36% reduction of the primary endpoint and a 45% reduction for ESRD at study end (45). In IDNT, every twofold increase in baseline proteinuria doubled the risk of the primary endpoint. Irrespective of treatment group, this risk was cut in half with every 50% reduction in proteinuria at 1 year (46). These results clearly supported the value of proteinuria as an intermediate outcome in patients with overt diabetic nephropathy. It must be noted that there are currently no outcome data supporting differences in renoprotection between ACEIs and ARBs. This was exemplified in the Diabetics Exposed to Telmisartan And enalapril (DETAIL) study, which compared the effects of enalapril and telmisartan in 250 patients with type 2 diabetes, hypertension and UAE between 11 and 999  $\mu\text{g/min}$ . and showed the two drugs having similar effects on GFR change, UAE, BP, and the rates of ESRD, cardiovascular events and all-cause mortality (47).

The scarcity of effective means to halt the progression of proteinuric CKD led to several research efforts to evaluate the effects of aggressive RAS blockade (37). Short-term randomized studies in patients with micro- or macroalbuminuria have shown that use of a single RAS-blocker in ultra-high dose (i.e. 2–3 times the maximum dose for hypertension) could reduce UAE more effectively than conventional doses without important side effects (48,49). Similarly, combination treatment of ACEIs and ARBs reduced proteinuria more than single blockade at maximum doses (50,51). However, the premature termination of the two outcome trials in this area has provided definite results against the use of combined RAS blockade. In particular, the Aliskiren Trial in Type-2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) study compared the effects of combination of aliskiren and ACEI or ARB versus ACE or ARB alone on cardiovascular and renal outcomes in 8561 patients with type 2 diabetes. ALTITUDE was prematurely terminated at 69% of events (52). The components of the primary outcome did not differ between groups, with the exception of resuscitated cardiac arrest; the main differences between groups was the proportion of patients with hyperkalaemia (11.2% vs. 7.2%), and hypotension (12.1% vs. 8.3%) ( $p < 0.001$  for both) (52). The Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) study aimed to randomize 1850 patients with diabetes, eGFR  $30\text{--}90\text{ mL/min/1.73 m}^2$  and ACR  $>300\text{ mg/day}$  to combination of losartan and lisinopril versus losartan alone. The study was stopped due to safety concerns after 1448 patients were randomized with a median follow-up of 2.2 years. No difference in the primary endpoint of eGFR change, ESRD or death (HR with combination therapy 0.88; 95% CI: 0.70–1.12;  $p = 0.30$ ) (Figure 57.1), mortality or cardiovascular events were noted with combination therapy, whereas risk of hyperkalaemia (6.3 vs. 2.6 events per 100 person-years  $p < 0.001$ ) was increased (53). The above results clearly indicate that use of combined use of ACEI with ARB or aliskiren is not indicated in CKD

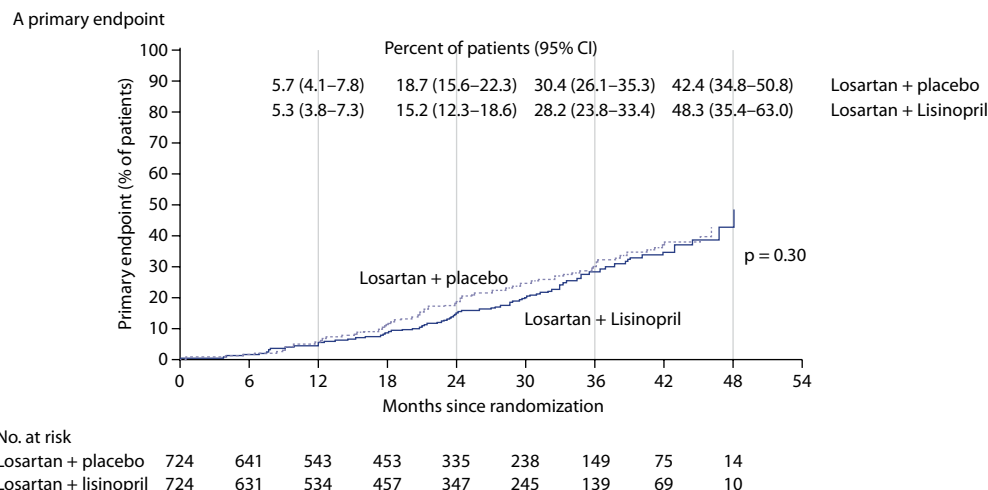


**Figure 57.1** Kaplan–Meier Plot of cumulative probabilities of the primary endpoint in the VA NEPHRON-D trial. The primary endpoint was the first occurrence of a change in the eGFR (decline of  $\geq 30$  mL/min/1.73 m<sup>2</sup> if the initial estimated GFR was  $\geq 60$  mL/min/1.73 m<sup>2</sup> or a decline of  $\geq 50\%$  if the initial estimated GFR was  $< 60$  mL/min/1.73 m<sup>2</sup>), end-stage renal disease or death. (From Fried LF et al. *N Engl J Med* 2013; 369: 1892–1903. With permission.)

patients. It should be noted, however, that since the main concern of this combination is hyperkalaemia leading to cardiac arrhythmias, it is not impossible for the issue to be re-examined in the future, given the recent release of well-tolerated potassium-lowering agents (54).

Addition of a mineralocorticoid-receptor-antagonist to patients already on ACEI or ARB is suggested as another option for renoprotection, since plasma aldosterone is elevated in CKD and may independently contribute to renal injury (55), whereas use of ACEIs or ARBs does not necessarily result in maintained reductions in plasma aldosterone (56). Addition of spironolactone in proteinuric patients receiving ACEIs or ARBs reduced proteinuria in several pilot studies (57–60). Similarly, eplerenone added to an ACEI further reduced UAE in patients with hypertension and left ventricular hypertrophy (LVH) (61). Increase of serum potassium to more than 5.5 mEq/L, is always a case of concern (62,63) and when such agents are used, serum potassium must be followed closely, and a dose adjustment of the concomitant conventional diuretic therapy should be considered. A detailed study randomized 81 patients with diabetes, hypertension and macroalbuminuria already on lisinopril 80 mg, to losartan 100 mg, spironolactone 25 mg or placebo for 48 weeks (64). Compared to placebo, ACR decreased by 34.0% with spironolactone and by 16.8% with losartan; ambulatory BP, creatinine clearance (CrCl), sodium and protein intake, and glycaemic control did not differ between groups. Serum potassium was higher with either spironolactone or losartan (yet on average  $< 5.2$  mEq/L in all groups). A new aldosterone-blocker with the potential for less hyperkalaemia, finerenone, was recently tested in 823 diabetic patients with micro- or macroalbuminuria randomized to finerenone 1.25, 2.5, 5, 7.5, 10, 15 and 20 mg/d or placebo for 90 days (65). ACR significantly decreased by 21%, 24%, 33% and 38% relative to baseline, whereas hyperkalaemia leading to discontinuation was up to 3.2% with finerenone. Based on the above promising findings, the

use of finerenone is currently tested in two outcome trials in individuals with diabetic CKD.

#### OTHER ANTIHYPERTENSIVE CLASSES

The two different subtypes of calcium channel blockers, non-dihydropyridine (non-DHPCCB) and dihydropyridine (DHPCCB) have been shown to have divergent effects on proteinuria. In patients with overt diabetic nephropathy, non-DHPCCBs (verapamil, diltiazem) were associated with reductions in proteinuria and the rate of CrCl decline that were greater than those with atenolol (66,67) and no different to those with lisinopril (66), with similar BP control in the various groups. In another cohort of patients with diabetic nephropathy, followed for 21 months, a DHPCCB, nifedipine XL, produced no change in proteinuria, whereas diltiazem resulted in a proteinuria reduction of about 60% (68). The mechanism for this difference relates to the fact that DHPCCBs produce afferent arteriole dilation (69). This relates to increased renal blood flow and gives the mistaken impression of preserved renal function but comes at the expense of further increased intraglomerular pressures and permeability to albumin, which leads to poorer long-term renal outcomes. Further evidence to support lack of renoprotective properties of DHPCCBs come from multicentre trials. As mentioned above, in the IDNT trial, amlodipine was associated with a 6% increase in proteinuria versus baseline and a 23% higher incidence of the primary endpoint compared to irbesartan (44). In the nondiabetic population of the AASK trial, the 58% increase in proteinuria seen at 6 months in those treated with amlodipine correlated with a greater incidence of the composite endpoint of a  $\geq 50\%$  reduction in GFR, ESRD and/or death when compared to those treated with ramipril who had a 20% reduction in proteinuria (70). Data from the REIN-2 study also question the ability of DHPCCBs to help towards regression of renal function deterioration in proteinuric kidney disease even by means of BP lowering (71). However, as noted also

above, a detrimental effect of DHPCCBs in renal progression is not apparent in patients without proteinuria and preserved eGFR, as noted in the ALLHAT trial (72) or in combination with ACEI, as noted in the ACCOMPLISH trial (73). Overall, these notions are in keeping with the aforementioned observations about ACE inhibitors, i.e. in advanced kidney disease with proteinuria the focus should be both BP and proteinuria reduction with the use of proper agents, whereas in early kidney disease the focus should be BP control (37).

As most patients with CKD and proteinuria would need a combination of two or more antihypertensive agents to reach the aforementioned BP goals, and renal function deterioration is accompanied with salt and water retention, diuretics are usually necessary in patients with CKD (6,37). It is not uncommon for BP to remain refractory to treatment without the use or with inappropriate dosing of diuretics (74). Although diuretics have not been directly shown to reduce urine proteinuria beyond the amount that is expected due to BP reduction, a potential benefit of diuretics relates to helping preserve the anti-proteinuric effects of ACEIs or ARBs, which are blunted with high-salt diets (75,76). Thiazide diuretics (with the exception of metolazone) become less effective when GFR falls below 40 mL/min/1.73 m<sup>2</sup> (77). In GFR below that level, a loop diuretic (i.e. furosemide, torsemide, etc.) is rather necessary. If furosemide is used, adequate dosing (i.e. 2–3 times instead of once-daily) is necessary to achieve optimal BP control, as it has a very short duration of action (3–6 h).

Finally, there is no direct evidence that conventional  $\beta$ -blockers provide additional renoprotective effects. In overt diabetic nephropathy non-DHPCCBs produced greater proteinuria reductions than atenolol (67,78). In patients with type 2 diabetes in the UKPDS 39 study there were not significant differences between captopril and atenolol in the level of BP achieved, incidence of overt nephropathy and doubling of creatinine, data suggesting that any renoprotective effect is due to BP lowering (79). The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial showed that carvedilol was associated with significant reductions in the risk of microalbuminuria development in hypertensive type 2 diabetic patients compared to metoprolol (80). These findings, however, were not confirmed by a trial in proteinuric CKD. Therefore,  $\beta$ -blockers are suggested to be used in patients with advanced CKD mainly for BP reduction (37). Second-line antihypertensive agents, such as  $\alpha$ -blockers, centrally acting agents and others, are also necessary in several patients with advanced CKD to achieve BP control.

## HYPERTENSION IN PATIENTS WITH ESRD UNDER DIALYSIS

### DEFINITION AND EPIDEMIOLOGY

Defining hypertension in ESRD patients under maintenance dialysis is challenging. In the 2005 NKF-KDOQI guidelines, hypertension was defined as pre-hemodialysis BP levels >140/90 mmHg or post-hemodialysis BP levels

>130/80 mmHg (6). However, observational studies suggest that peridialytic BP measurements have a flat or 'U' curve association with cardiovascular events or mortality, with hazard ratios not increasing at the SBP range of 110–180 mmHg, in contrast to what is expected from observations in the general hypertensive population (81). Previous studies suggested that low BP in hemodialysis is associated with early mortality and deaths of primarily noncardiac origin, indicating poor physiological reserve and frailty due to comorbid conditions (82). However, these findings largely reflect the poor validity of peridialytic BP recordings *per se* to describe the true BP load, due to reasons ranging from inadequate implementation of standardized measurement techniques to the well-documented BP fluctuations during the interdialytic BP interval (83–85). Indeed, BP measurements pre-, during and post-dialysis are not made for diagnostic reasons but to exploit a major hemodynamic metric like BP in order to assess cardiovascular stability before, during and immediately after the dialysis procedure (86). Factors leading to inaccurate BP pre- and post-hemodialysis readings may include white-coat effect, limited time for fear or anxiety for correct arteriovenous fistula needling, previous bilateral upper limb attempts of arteriovenous fistulae and unknown validity of most oscillometric devices attached to commercially available hemodialysis machines. Furthermore, the intermittent nature of hemodialysis as a form of renal replacement therapy is long known to be associated with wide fluctuations in a wide range of metabolic, electrolyte and hemodynamic parameters (87), including a particular pattern of BP changes during the interdialytic interval in the majority of patients, with progressive increase in BP during the interdialytic interval and rapid decrease during the dialysis session following sodium and water accumulation and removal, respectively. Thus, truly high BP variability (pre- to post-dialysis and day-by-day variability) in response to fluctuations in volume status and other parameters during the intra- and interdialytic periods, is another important issue that complicates the accurate diagnosis of hypertension (88). Defining hypertension with predialysis BP becomes even more complex in the 5–15% of patients having the 'paradoxical' phenomenon of intradialytic hypertension, i.e. increase in BP during or immediately after hemodialysis (89).

In contrast to the above, elevated SBP measured at home or with ABPM monitoring has been associated with target-organ damage, such as LVH, as well as mortality (84,90–92). The use of ABPM has also the advantage of recording BP during nighttime, which is particularly relevant, as the presence of a non-dipping nocturnal BP pattern is very common among dialysis patients and has been associated with LVH (88,93) and increased risk of all-cause and cardiovascular mortality (94). Thus, many experts suggest that ABPM is the gold-standard method for the diagnosis and management of hypertension in hemodialysis patients, which should be probably the first population where BP definition should not be based on office recordings (83,84,95,96). To this end, a recent consensus paper on hypertension in hemodialysis patients, which embodies a joint effort of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) and the European Society of Hypertension (ESH), proposed a definition for

hypertension based on out-of-dialysis BP measurements (Table 57.3) (86).

### EPIDEMIOLOGY OF HYPERTENSION IN HEMODIALYSIS PATIENTS

Previous efforts on hypertension prevalence in dialysis defined hypertension based on peridialytic BP measurements (86). Using definitions for hypertension such as pre-hemodialysis MAP  $\geq 114$  mmHg or use of antihypertensive agents (97), pre-hemodialysis SBP  $\geq 140$  mmHg and/or DBP  $\geq 90$  mm (98) and 1-week average pre-hemodialysis SBP  $> 150$  mmHg and/or DBP  $> 85$  mmHg, or use of antihypertensive agents (99) prevalence was estimated to 70–88%, while concordant control was achieved at 30–70% (86). A previous study on the prevalence of hypertension in 369 African American hemodialysis patients using ABPM (44-hour interdialytic ambulatory SBP  $\geq 135$  mmHg and/or DBP  $\geq 85$  mmHg or use of antihypertensive medications) found that 82% of the patients were hypertensives, and control of hypertension was achieved only in 38% of these patients (100). The only information on a Caucasian population comes from a recent study in 160 hemodialysis patients from our group, where the prevalence of hypertension (defined as SBP  $\geq 130$  or DBP  $\geq 80$  mmHg during the 44-hour interdialytic period or use of antihypertensive agents) was 88.8% and 19.6%, and 11.5% had white-coat effect or masked hypertension accordingly (101).

### EPIDEMIOLOGY OF HYPERTENSION IN PERITONEAL DIALYSIS PATIENTS

The prevalence of hypertension among patients on peritoneal dialysis was evaluated in a cross-sectional study (102). Using the WHO/ISH 1999 definition of hypertension (SBP  $\geq 140$  or DBP  $\geq 90$  mmHg, or use of antihypertensive

treatment), the prevalence of hypertension was 88%. When defining hypertension using a BP load of more than 30% of values  $> 140/90$  at daytime or  $> 120/80$  at nighttime during 24-hour ABPM, the estimated prevalence was 69%. The average 24-hour BP in this study was  $139 \pm 19/81 \pm 11$  mmHg, suggesting again that if the currently proposed definition of average SBP  $\geq 135$  and/or DBP  $\geq 85$  mmHg in ABPM or antihypertensive treatment (103) was used instead, hypertension prevalence would also exceed 70–80% (102). Of note, 53% of patients in this study were non-dippers and an additional 9% were reverse-dippers. Small studies comparing the ambulatory BP profile between patients treated with automated peritoneal dialysis (APD) versus continuous ambulatory peritoneal dialysis (CAPD) showed that the average 24-hour BP did not differ between the treatment modalities (104,105). Volume overload is frequently more marked in peritoneal dialysis than in hemodialysis patients (106) and these patients require antihypertensive drugs more frequently (65%) than hemodialysis patients (38%,  $p < 0.001$ ). In this regard, a strict volume control policy could reduce the need of antihypertensive medication also in peritoneal dialysis patients. As the cyclic variations in volume status and in several other metabolic parameters in patients receiving peritoneal dialysis are absent, it has been hypothesized that BP control and BP diurnal variation may be substantially different compared to hemodialysis. One study testing this hypothesis (107) compared the 44-hour BP profile of 22 hemodialysis patients with that of 24 patients treated with CAPD, showing mean 44-hour SBP and DBP to be similar between the groups, but daytime BP on the dialysis day was lower and nighttime BP on the dialysis-off day to be higher in hemodialysis patients. Further, a dipping pattern was much lower in hemodialysis patients (18% vs. 88%) (107). Another study including 33 hemodialysis and 27 peritoneal dialysis patients showed that diurnal BP pattern (i.e. dipping

**Table 57.3** Diagnosis of hypertension in dialysis patients proposed by the EURECA-m working group of the ERA-EDTA and the Hypertension and the Kidney working group of the ESH

Hypertension in dialysis patients should be defined on the basis of home BP or ABPM measurements, as follows:

- Home BP in hemodialysis: An average BP  $\geq 135/85$  mmHg for measurements collected in the morning and in the evening over 6 non-dialysis days (covering a period of 2 weeks). Measures should be performed in a quiet room, with the patient in seated position, back and arm supported, after 5 minutes of rest, and with two measurements per occasion taken 1–2 minutes apart.
- Home BP in peritoneal dialysis: An average BP  $\geq 135/85$  mmHg over 7 consecutive days with measurements collected as above.
- ABPM in hemodialysis: An average BP  $\geq 130/80$  mmHg over 24-hour monitoring during a mid-week day free of hemodialysis. Whenever feasible ABPM should be extended to 44-hours, i.e. covering a whole mid-week dialysis interval.
- ABPM in peritoneal dialysis: An average BP  $\geq 130/80$  mmHg over 24-hour monitoring.
- For hemodialysis patients no recommendation can be made on the basis of pre-dialysis or post-dialysis BP. When neither ABPM nor home BP measurements are available in these patients, the diagnosis can be made on the basis of office BP measurements taken during the dialysis interval, i.e. the average of three measurements with 1–2 minutes interval obtained in the sitting position by trained personnel after at least 5 minutes of quiet rest. The threshold of office BP  $\geq 140/90$  mmHg recommended by current guidelines for the definition of hypertension in CKD patients can be used for hemodialysis patients.
- For peritoneal dialysis patients, office BP  $\geq 140/90$  mmHg obtained as described immediately above can be used for the diagnosis of hypertension.

Source: Modified from Sarafidis PA et al. *J Hypertens* 2017; 35: 657–676. With permission.

Abbreviations: BP, blood pressure; ABPM, ambulatory blood pressure monitoring; EURECA-m, European Renal and Cardiovascular Medicine working group; ERA-EDTA, European Renal Association-European Dialysis and Transplant Association; ESH, European Society of Hypertension.



status) did not differ between the two modalities over an approximately 48-hour BP recording, but average ambulatory SBP ( $142.1 \pm 16.3$  vs.  $130.4 \pm 17.1$  mmHg,  $p < 0.01$ ) and SBP loads were higher in those receiving hemodialysis (108). The above studies are small, limited by inadequate matching of patients; thus newer studies with ABPM are necessary for any conclusions to be drawn.

## PATHOGENESIS

The major pathophysiologic mechanism of hypertension development in hemodialysis patients is sodium and water overload (8). In CKD, the kidney's ability to control water and sodium homeostasis is severely impaired, particularly in hemodialysis patients with little or no residual renal function (109). Due to the intermittent nature of renal replacement therapy, hemodialysis patients are subjected to sodium and fluid accumulation and BP elevation in proportion to weight gain during the interdialytic interval, a phenomenon superimposed on BP circadian variation (110–112). The inter-dialysis increase in BP is not limited to brachial BP but extends to other critical hemodynamic parameters like aortic BP (110), and the peripheral and central BP burden is accentuated during the long dialysis interval, again in proportion to fluid overload (112,113). Until fluid and sodium overload is removed during dialysis, a rise in peripheral vascular resistance would sustain hypertension in these individuals.

Sympathetic overactivity is another major cause of hypertension in ESRD. Efferent sympathetic discharge rate is doubled in hemodialysis patients with in situ native kidneys but normal in hemodialysis patients after bilateral nephrectomy (114). Bilateral nephrectomy of failed kidneys produces sustained reductions in peripheral vascular resistance and dramatic BP decrease (115). Recent observations where renal denervation substantially reduced BP in small series of hemodialysis patients with severe resistant hypertension support the above (116,117). Activation of RAS is also involved, as clinical studies show increase in plasma renin activity (PRA) and plasma aldosterone from pre- to post dialysis, suggesting that residual functioning nephrons in dialysis patients retain their ability to sense acute changes in sodium intravascular volume status in response to ultrafiltration (118,119). Overactivation of SNS and RAS may be particularly relevant for patients with intradialytic hypertension (89).

Arterial stiffness is particularly accelerated in ESRD patients and is independently associated with high systolic BP, LVH and increased all-cause and cardiovascular mortality in hemodialysis patients (120,121). An analysis including 125 hemodialysis patients showed that log of PWV presented linear relationship with BP (each log increase in PWV was associated with 20.3, 7.2 and 12.8-mmHg increases in SBP, DBP and PP [pulse pressure], respectively), but also increasing PWV blunted the circadian amplitude of SBP and PP (122). A study evaluating acute changes in arterial stiffness indexes during the interdialytic periods showed that augmentation index (AIx) and central PP is increased during both 3-day and 2-day interdialytic intervals; aortic and brachial PWV was unchanged in these short time frames. The increase in AIx was 30% greater during the 3-day than during the 2-day interval and was associated with interdialytic

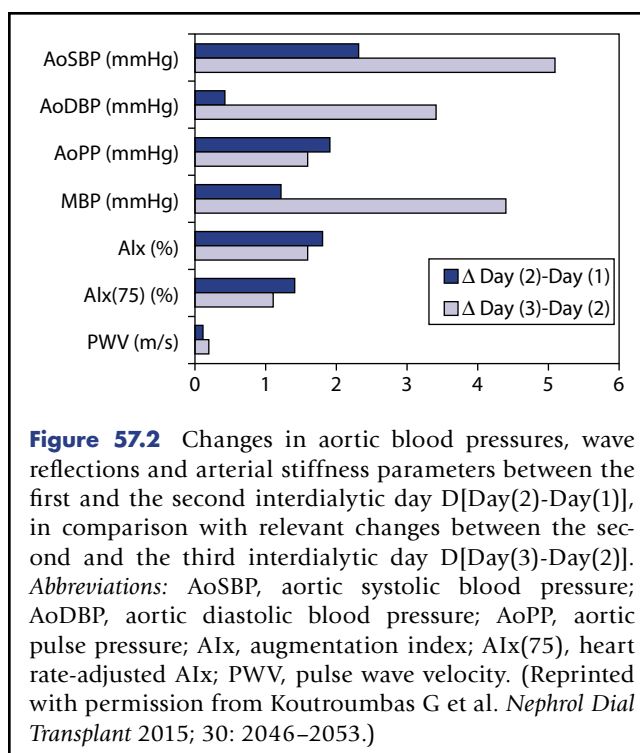


**Figure 57.2** Changes in aortic blood pressures, wave reflections and arterial stiffness parameters between the first and the second interdialytic day D[Day(2)-Day(1)], in comparison with relevant changes between the second and the third interdialytic day D[Day(3)-Day(2)]. Abbreviations: AoSBP, aortic systolic blood pressure; AoDBP, aortic diastolic blood pressure; AoPP, aortic pulse pressure; AIx, augmentation index; AIx(75), heart rate-adjusted AIx; PWV, pulse wave velocity. (Reprinted with permission from Koutroumbas G et al. *Nephrol Dial Transplant* 2015; 30: 2046–2053.)

weight gain (113). Subsequent studies with ABPM recordings from our group further confirmed the above, showing a continuous increase in wave reflection indices and central BP in both the 2-day and 3-day interdialytic intervals with minimal increase in PWV (110,112). Of note, the above findings were associated with a greater increase in aortic SBP and DBP when moving from the second to the third than when moving from the first to the second day of the large intradialytic interval, suggesting a progressive BP increase with increasing time from the last dialysis (Figure 57.2) (112).

Endothelial dysfunction could also cause BP elevation in ESRD. Patients with CKD show markedly reduced NO-dependent vasodilation, possibly due to reduced production of NO (123). This reduction in NO bioavailability in ESRD may result from high circulating levels of asymmetric dimethylarginine (ADMA), an endogenous NO synthase inhibitor (124). Other mechanisms involved in hypertension occurrence in hemodialysis patients include sleep apnoea, which provokes nocturnal hypoxemia and sympatheticotonia (89), as well as the use of medications which induce BP elevation, such as erythropoietin-stimulating agents (8).

## TREATMENT OF HYPERTENSION IN PATIENTS ON DIALYSIS

Management of hypertension in dialysis patients is complex. Focusing on correction of the primary pathogenetic mechanism, i.e. sodium and volume excess, by carefully implementing a series of non-pharmacological measures in order to achieve the dry weight for each individual patient and to avoid intradialytic sodium loading, is considered central (Table 57.4). However, since 95% of patients are already hypertensive and the vast majority are receiving



**Table 57.4** Non-pharmacological measures to reduce sodium and volume overload in hemodialysis

- Achievement of dry-weight of each patient
- Minimization of sodium gain
- Restriction of interdialytic sodium consumption to <65 mmol (1.5 g of sodium or 4 g of sodium chloride) per day
- Individualization of dialysate sodium according pre-dialysis serum sodium
- Avoidance of sodium-containing or sodium-exchanging drugs
- Ensuring adequate (i.e. at least 4 hours) dialysis duration

antihypertensive agents when dialysis is initiated, and common antihypertensive agents may be prescribed for other indications (i.e.  $\beta$ -blockers for angina symptoms, heart failure or rate control, RAS blockers for heart failure, etc.), careful handling of antihypertensive drugs when dry weight is pursued is required (86).

### NON-PHARMACOLOGIC MEASURES FOR THE MANAGEMENT OF HYPERTENSION IN DIALYSIS

Achievement of the correct dry weight is fundamental in ensuring BP control in hemodialysis patients (125). Previous studies have shown that in hemodialysis patients normotension can be achieved by lowering dry weight (126). In 876 incident hemodialysis patients, 90% of whom had hypertension, a significant 20-mmHg reduction in pre-hemodialysis mean arterial pressure was achieved with a mean reduction of post-hemodialysis weight by 2 kg within a month (127). BP levels were gradually further decreased within 12 months follow-up time, with no further dry weight reductions (127), and these changes were attributed to the delayed restoration of peripheral vascular resistance, which were previously increased due to chronic water accumulation and high BP levels, a phenomenon known as 'lag phenomenon' (125). The value of careful ultrafiltration intensification is supported by the Dry weight Reduction in Hypertensive Hemodialysis Patients (DRIP) study (128), which randomized 100 hemodialysis patients in two groups, one of dry weight probing (of 0.9 kg reduction of dry weight on average over a period of 4 weeks) and one of standard care. A significant reduction in ambulatory SBP/DBP by 11/6 mmHg was achieved in patients in the active arm. Of note, reductions in SBP were not associated with the presence or absence of pedal oedema in these patients (128). Results from another case-control study including 394 hemodialysis patients indicated that dry weight reduction was associated with lower left ventricular mass and better left ventricular systolic and diastolic function, regardless of BP changes (129). Dry weight probing should be prescribed with caution, as the occurrence of intradialytic hypotension and hypotension-related cerebrovascular events, access-related complications and reduction of residual urine output may implicate excessive dehydration due to ultrafiltration. It should be remembered, however, that hypotensive episodes during hemodialysis are increasing in parallel with the number of antihypertensive medications and must not be an obstacle to achieve dry weight (130). It must also be noted that an

accurate and objective method of dry weight estimation or evaluation of volume overload is still not available, and as its reliance on physical examination may be misleading (131), physicians may stop dry weight probing in several patients due to the fear of hypotensive episodes. A combination of methods such as bioimpedance analysis, relative blood volume monitoring and lung ultrasound are expected to provide a more precise estimate of fluid accumulation in critical organs and thus help towards objective definition of dry weight (132,133).

Reduction of dietary sodium is considered important in decreasing sodium overload and managing BP levels in hemodialysis. Physicians pay attention to fluid consumption without focusing on the daily dietary sodium intake, which is the key element promoting thirst in dialysis (134). Excessive salt consumption is independently associated with higher interdialytic weight gain (135), while significant improvements in BP levels and LVH can be achieved in hemodialysis patients by restricting daily salt consumption to 1.5 g (103,136). Prescribing higher dialysate sodium to avoid hemodynamic instability during sessions leads to higher post-hemodialysis serum sodium concentrations and higher interdialytic weight gain, promoting a vicious cycle (136). Lowering or individualizing dialysate sodium can be helpful towards this matter (103,125), as a cross-over study showed higher interdialytic ambulatory SBP by prescribing elevated dialysate sodium concentration at 147 mEq/dL (137). Another study in 16 hemodialysis patients showed that reducing dialysate conductivity to 13.5 mS/cm, so that patient's post-dialysis plasma sodium concentrations are 135.6 mEq/L, decreased pre-dialysis BP levels by 11/4 mmHg (138). It is strongly advised by the chief medical officers of US dialysis providers to incorporate dialysate sodium concentrations set routinely in a range of 134–138 mEq/L and avoid the use of hypertonic saline dialysates compared to patients' pre-hemodialysis serum sodium concentration (139).

Another main way to efficiently remove excess salt and water is to provide adequate time of dialysis (86). Nonadherence to the minimum recommended schedule of three sessions of 4 hours per week is associated with lower rates of BP control (140). Increasing the duration of dialysis is particularly beneficial in those who remain hypertensive despite the intensification of volume withdrawal, or who experience frequent episodes of intradialytic hemodynamic instability (141). Several studies showed that patients assigned to longer (i.e. up to 8 hours thrice weekly) or more frequent (i.e. up to 6 times per week) dialysis regimens achieve better BP control with reduced requirements for antihypertensive medications, a benefit that is possibly mediated through better correction of sodium and volume excess or less SNS and RAS stimulation (141–144). A long-term, observational post-trial analysis of the daily in-centre trial of the Frequent Hemodialysis Network (145) showed a lower risk of death in patients originally randomized to frequent hemodialysis of 6 times a week and 1.5–2.75 h/session (16%) as compared to those randomized to conventional hemodialysis treatment (28%). This was not evident in a similar analysis of the twin Nocturnal Trial, where mortality was largely increased in the frequent hemodialysis group (6 times a week >6 h/session) (146); of note, the most prominent difference between groups in the main Nocturnal Trial seemed to be the faster loss of residual diuresis in the frequent dialysis arm (147). Overall, ensuring three 4-hour

dialysis sessions is necessary to ensure BP control in these patients (134).

### USE OF ANTIHYPERTENSIVE AGENTS IN PATIENTS ON DIALYSIS

After the above strategies are properly implemented, the introduction of drug treatment can further help in achieving the optimum BP. All major antihypertensive classes with the exception of diuretics can be considered in hypertension management in hemodialysis patients (103,148), as the use of agents from these classes was associated with reduced cardiovascular risk (Table 57.5). The choice of a specific antihypertensive drug should be based on the patient's comorbid conditions and the pharmacologic characteristics of the agent, including dialyzability (134). None of the antihypertensive classes has been proven superior in controlling BP levels compared to another (149), as no comparative studies with the use of ABPM exist. Further, no study has compared the effectiveness of antihypertensive treatment with that of strict control of water and sodium balance with non-pharmacologic measures (125). However, accumulated evidence from clinical trials suggests that the BP-lowering effect of antihypertensive drug treatment was associated with significant improvement in cardiovascular mortality in patients undergoing hemodialysis. Results from a systematic review of five randomized controlled studies indicated that among 1202 patients, those receiving drug treatment (ACEI, ARB,  $\beta$ -blocker or CCB) had 31% lower risk of cardiovascular events occurrence and all-cause mortality compared to those not receiving drugs or receiving placebo (150). In another meta-analysis of eight randomized controlled trials including 1679 patients, it was shown that lowering SBP by 4.5 mmHg and DBP by 2.3 mmHg with the use of ACEI, ARB,  $\beta$ -blocker or CCB was associated with 29% lower cardiovascular and all-cause mortality (151).

### BLOCKERS OF THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

The RAS blockers class is used as in hemodialysis patients, mostly due to continuation of hypertension treatment before dialysis, or for other comorbidities. However, their

effect on cardiovascular outcomes is examined in relatively few studies, as in the case of other antihypertensive classes (86,134). One randomized study (Fosinopril in Dialysis [FOSIDIAL]) has prospectively evaluated the effects of fosinopril (up to 20 mg/day t.i.d) and placebo therapy on cardiovascular events (152). Almost 400 hemodialysis patients with or without hypertension but with LVH were included and followed-up for 4 years. Hypertensive patients on fosinopril had a higher drop in pre-dialysis SBP (fosinopril 11.7; placebo 5.4 mmHg;  $p = 0.002$ ), but hazard ratios for the primary endpoint of fatal and non-fatal CV events was similar between the fosinopril and placebo groups (RR: 0.93; 95% CI: 0.68–1.26) (152). In a meta-analysis of smaller studies comparing RAAS blockers versus other classes, placebo or no treatment in hemodialysis found similar hazard ratios for the two patient groups (153). From the three studies included in this meta-analysis, the first randomized 80 patients to candesartan (4–8 mg/day) or nothing, and after 19 months patients on candesartan had significantly lower cardiovascular events and mortality (16.3% vs. 45.9%,  $p < 0.01$  and 0% vs. 18.9%,  $p < 0.001$ , respectively) (154). Another open-label study randomized 360 hemodialysis patients with hypertension to ARB or nothing. No difference was noted in pre-hemodialysis BP changes between the start and the end of the study in the two study arms, but ARB use was associated with lower cardiovascular event occurrence (HR 0.51; 95% CI: 0.33–0.79) (155). Finally, in a more recent study, 469 hypertensive hemodialysis patients were randomly assigned to olmesartan (10–40 mg/day) or other treatment, but olmesartan was not associated with significant reductions in cardiovascular risk (HR 1.00; 95% CI: 0.71–1.40) or mortality (HR 0.97; 95% CI: 0.62–1.52) (156). Overall, a superiority of ACEIs and ARBs over other antihypertensive drugs has not been demonstrated until now in dialysis patients, and antihypertensive treatment per se rather than the use of a RAS-blocker could be the factor reducing cardiovascular risk (86). Importantly, almost all ARBs are not dialyzed and do not require dosage modification in dialysis, whereas ACEIs have differences regarding their dialyzability.

The effect of mineralocorticoid-receptor antagonists (MRAs) in hemodialysis patients compared to other

**Table 57.5** Outcome trials with major antihypertensive classes in patients on dialysis

|                                    |                                                                                                                                                                                                                                                                                                                                  |
|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>ACE-inhibitors</b>              | In the FOSIDIAL trial in HD patients with LVH (152) fosinopril did not reduce cardiovascular events and mortality compared to placebo.                                                                                                                                                                                           |
| <b>ARBs</b>                        | In HD patients, losartan/valsartan/candesartan reduced cardiovascular events and mortality compared to treatment not including ACEIs/ARBs (154,155).<br>In the OCTOPUS trial in HD patients with hypertension (156), olmesartan did not reduce cardiovascular events or mortality compared to treatment not including ACEIs/ARBs |
| <b>MRAs</b>                        | In two trials in HD and PD patients, spironolactone reduced cardiovascular events and mortality compared to no additional treatment or placebo (158,159).                                                                                                                                                                        |
| <b><math>\beta</math>-blockers</b> | In HD patients with dilated cardiomyopathy carvedilol reduced mortality compared to placebo (161).<br>In the HDPAL trial in HD patients with hypertension and LVH (162) thrice-weekly atenolol reduced cardiovascular events compared to thrice-weekly lisinopril.                                                               |
| <b>Calcium channel blockers</b>    | In HD patients with hypertension amlodipine reduced cardiovascular events compared to placebo (165).                                                                                                                                                                                                                             |

Abbreviations: FOSIDIAL, Fosinopril in Dialysis trial; HD, hemodialysis; HDPAL, Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril trial; LVH, left ventricular hypertrophy; OCTOPUS, Olmesartan Clinical Trial in Okinawa Patients under Dialysis Study; PD, peritoneal dialysis.

antihypertensive drugs classes has also recently been studied. A study of 76 dialysis patients with refractory hypertension randomized subjects to 12-week treatment with spironolactone (25 mg/day) or placebo and showed reduced 24-hour ambulatory BP by 12.5/7 mmHg in the spironolactone group (157). The Dialysis Outcomes Heart Failure Aldactone study (DOHAS) compared the effects of adding 25 mg of spironolactone versus standard of care in 309 hemodialysis patients (158). After 3 years, spironolactone greatly reduced the risk of death or hospitalization for cardiovascular event (HR 0.38; 95% CI: 0.17–0.83), without significantly lowering BP levels from baseline to the end of the study. The incidence of drug discontinuation due to serious hyperkalaemia was 1.9% (158). Another study randomized 253 non-heart failure patients receiving hemodialysis or peritoneal dialysis to 25 mg of spironolactone or placebo. Again, spironolactone impressively reduced the composite primary endpoint of cardiovascular events (HR 0.42; 95% CI: 0.26–0.78) (159).

### β-BLOCKERS

β-blockers are characterized by a wide variability in dialyzability; i.e. atenolol is 50% dialyzed, metoprolol is fully dialyzed, while carvedilol and labetalol are not removed during hemodialysis (160). A randomized study in 114 hemodialysis patients with dilated cardiomyopathy examined the effect of carvedilol (25 mg twice a day, up to the highest dose tolerated) on cardiovascular events and survival during a 2-year follow-up (161). All-cause mortality (HR 0.51; 95% CI: 0.32–0.82), cardiovascular mortality (HR 0.32; 95% CI: 0.18–0.57) and hospital admissions (HR 0.44; 95% CI: 0.25–0.77) were significantly lower with carvedilol than placebo, accompanied by a significant decrease by 14/5 mmHg in BP levels in the active arm (161). In the Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril (HDPAL) trial, 200 hemodialysis patients with hypertension and LVH were randomized to lisinopril or atenolol administered three times per week after hemodialysis (162). The study was prematurely terminated due to superiority of atenolol over lisinopril in terms of cardiovascular outcomes (incidence of MI, stroke, heart failure and cardiovascular death was higher in the lisinopril group, RR: 2.36; 95% CI: 1.36–4.23). Importantly, significant differences were observed in the 44-hour BP reduction and the left ventricular mass index between the two study groups (162). A recent retrospective cohort study showed that a survival advantage may not be offered by highly dialyzable β-blockers, possibly because of lack of intradialytic protection against arrhythmias due to rapid removal with dialysis; thus a non-dialyzable β-blocker could be more reasonable choice (86,163).

### CALCIUM CHANNEL BLOCKERS

An earlier double-blind randomized study examined the antihypertensive effect of CCBs in hemodialysis patients. After 24 weeks, patients receiving nitrendipine had a significant reduction of  $16.7 \pm 21.2$  mmHg in SBP levels during hemodialysis versus placebo (164). A subsequent outcome study randomized 251 hypertensive hemodialysis patients to amlodipine (5–10 mg/day) or placebo over a 30-month period (165). Amlodipine insignificantly improved survival compared with placebo, but significantly reduced the composite secondary endpoint of all-cause death, nonfatal stroke, MI, coronary revascularization and angioplasty for

peripheral vascular disease (H: 0.53; 95% CI: 0.31–0.93) (165). At the end of this study pre-hemodialysis BP was significantly lower in the amlodipine study group compared to baseline, but not in placebo; occurrence of hypotensive episodes was similar between the two groups (165). Importantly, CCBs are practically not removed during standard hemodialysis and their pharmacokinetics are unchanged in ESRD and thus can be dosed once-daily in these patients (160). Data on non-DHPCCB in hemodialysis patients are practically absent; their use should at least follow the recommendations for the general population (86).

### REFERENCES

- Coresh J, Byrd-Holt D, Astor BC et al. Chronic kidney disease awareness, prevalence, and trends among U.S. adults, 1999 to 2000. *J Am Soc Nephrol* 2005; 16: 180–188.
- Drey N, Roderick P, Mullee M, Rogerson M. A Population-based study of the incidence and outcomes of diagnosed chronic kidney disease. *Am J Kidney Dis* 2003; 42: 677–684.
- Saran R, Li Y, Robinson B et al. US Renal Data System 2015 annual data report: Epidemiology of kidney disease in the United States. *Am J Kidney Dis* 2016; 67: Svi, S1–305.
- Sarafidis PA, Li S, Chen SC et al. Hypertension awareness, treatment, and control in chronic kidney disease. *Am J Med* 2008; 121: 332–340.
- Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988–2008. *JAMA* 2010; 303: 2043–2050.
- K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis* 2005; 45: S1–153.
- K/DOQI Workgroup. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl* 2012; 2: 337.
- Sarafidis PA, Bakris GL. Kidney disease and hypertension. In: Lip G, Hall J (eds) *Comprehensive Hypertension*. Elsevier, London; 2007.
- James PA, Oparil S, Carter BL et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311: 507–520.
- Klag MJ, Whelton PK, Randall BL et al. Blood pressure and end-stage renal disease in men. *N Engl J Med* 1996; 334: 13–18.
- Peralta CA, Weekley CC, Li Y, Shlipak MG. Occult chronic kidney disease among persons with hypertension in the United States: Data from the National Health and Nutrition Surveys 1988–1994 and 1999–2002. *J Hypertens* 2013; 31: 1196–1202.
- Sarafidis PA, Sharpe CC, Wood E et al. Prevalence, patterns of treatment, and control of hypertension in predialysis patients with chronic kidney disease. *Nephron Clin Pract* 2012; 120: c147–c155.
- Gorostidi M, Sarafidis PA, de la Sierra A et al. Differences between office and 24-hour blood pressure control in hypertensive patients with CKD: A 5,693-patient cross-sectional analysis from Spain. *Am J Kidney Dis* 2013; 62: 285–294.
- Burnier M, Wuerzner G. Pathophysiology of hypertension. In: Jagadeesh G, Balakumar P, Maung UK (eds). *Pathophysiology and Pharmacotherapy of Cardiovascular Disease*. Springer International Publishing, Cham; 2015: 655–683.
- Mailloux LU, Levey AS. Hypertension in patients with chronic renal disease. *Am J Kidney Dis* 1998; 32: S120–S141.
- Burnier M, Coltamai L, Maillard M, Bochud M. Renal sodium handling and nighttime blood pressure. *Semin Nephrol* 2007; 27: 565–571.
- Whelton PK, Carey RM, Aronow WS et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2017.
- Sarafidis PA, Ruilope LM. Aggressive blood pressure reduction and renin-angiotensin system blockade in chronic kidney disease: Time for re-evaluation? *Kidney Int* 2014; 85: 536–546.
- Sarafidis PA, Lazaridis AA, Ruiz-Hurtado G, Ruilope LM. Blood pressure reduction in diabetes: Lessons from ACCORD, SPRINT



- and EMPA-REG OUTCOME. *Nat Rev Endocrinol* 2017; 13: 365–374.
20. Mancia G, De Backer G, Dominiczak A et al. 2007 ESH-ESC practice guidelines for the management of arterial hypertension: ESH-ESC task force on the management of arterial hypertension. *J Hypertens* 2007; 25: 1751–1762.
  21. Chobanian AV, Bakris GL, Black HR et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC 7 report. *JAMA* 2003; 289: 2560–2572.
  22. Klahr S, Levey AS, Beck GJ et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med* 1994; 330: 877–884.
  23. Peterson JC, Adler S, Burkart JM et al. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Ann Intern Med* 1995; 123: 754–762.
  24. Jafar TH, Stark PC, Schmid CH et al. Progression of chronic kidney disease: The role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: A patient-level meta-analysis. *Ann Intern Med* 2003; 139: 244–252.
  25. Sarnak MJ, Greene T, Wang X et al. The effect of a lower target blood pressure on the progression of kidney disease: Long-term follow-up of the modification of diet in renal disease study. *Ann Intern Med* 2005; 142: 342–351.
  26. Wright JT, Jr., Bakris G, Greene T et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK trial. *JAMA* 2002; 288: 2421–2431.
  27. Lea J, Greene T, Hebert L et al. The relationship between magnitude of proteinuria reduction and risk of end-stage renal disease: Results of the African American study of kidney disease and hypertension. *Arch Intern Med* 2005; 165: 947–953.
  28. Appel LJ, Wright JT, Jr., Greene T et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010; 363: 918–929.
  29. Sarafidis PA, Ruilope LM. Blood pressure targets in CKD and diabetes. *ESH Newsletter* 2013; 55.
  30. Bakris GL, Weir MR, Shanifar S et al. Effects of blood pressure level on progression of diabetic nephropathy: Results from the RENAAL study. *Arch Intern Med* 2003; 163: 1555–1565.
  31. Pohl MA, Blumenthal S, Cordonnier DJ et al. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: Clinical implications and limitations. *J Am Soc Nephrol* 2005; 16: 3027–3037.
  32. Sarafidis PA, Alexandrou ME, Ruilope LM. A review of chemical therapies for treating diabetic hypertension. *Expert Opin Pharmacother* 2017; 18: 909–923.
  33. Wright JT Jr, Williamson JD, Whelton PK et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; 373: 2103–2116.
  34. Cheung AK, Rahman M, Reboussin DM et al. Effects of intensive BP control in CKD. *J Am Soc Nephrol* 2017; 28: 2812–2823.
  35. Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1281–1357.
  36. Sarafidis PA, Bakris GL. Resistant hypertension: An overview of evaluation and treatment. *J Am Coll Cardiol* 2008; 52: 1749–1757.
  37. Sarafidis PA, Khosla N, Bakris GL. Antihypertensive therapy in the presence of proteinuria. *Am J Kidney Dis* 2007; 49: 12–26.
  38. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet* 1997; 349: 1857–1863.
  39. Hou FF, Zhang X, Zhang GH et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 2006; 354: 131–140.
  40. Jafar TH, Schmid CH, Landa M et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Intern Med* 2001; 135: 73–87.
  41. Sarafidis PA, Bakris GL. Antihypertensive therapy and the risk of new-onset diabetes. *Diabetes Care* 2006; 29: 1167–1169.
  42. Strippoli GF, Craig M, Deeks JJ et al. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: Systematic review. *BMJ* 2004; 329: 828.
  43. Brenner BM, Cooper ME, de Zeeuw D et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; 345: 861–869.
  44. Lewis EJ, Hunsicker LG, Clarke WR et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; 345: 851–860.
  45. de Zeeuw D, Remuzzi G, Parving HH et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: Lessons from RENAAL. *Kidney Int* 2004; 65: 2309–2320.
  46. Atkins RC, Briganti EM, Lewis JB et al. Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. *Am J Kidney Dis* 2005; 45: 281–287.
  47. Barnett AH, Bain SC, Bouter P et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004; 351: 1952–1961.
  48. Rossing K, Schjoedt KJ, Jensen BR et al. Enhanced renoprotective effects of ultrahigh doses of irbesartan in patients with type 2 diabetes and microalbuminuria. *Kidney Int* 2005; 68: 1190–1198.
  49. Hollenberg NK, Parving HH, Viberti G et al. Albuminuria response to very high-dose valsartan in type 2 diabetes mellitus. *J Hypertens* 2007; 25: 1921–1926.
  50. Schjoedt KJ, Astrup AS, Persson F et al. Optimal dose of lisinopril for renoprotection in type 1 diabetic patients with diabetic nephropathy: A randomised crossover trial. *Diabetologia* 2009; 52: 46–49.
  51. Mogensen CE, Neldam S, Tikkanen I et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: The candesartan and lisinopril microalbuminuria (CALM) study. *BMJ* 2000; 321: 1440–1444.
  52. Parving HH, Brenner BM, McMurray JJ et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012; 367: 2204–2213.
  53. Fried LF, Emanuele N, Zhang JH et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013; 369: 1892–1903.
  54. Sarafidis PA, Georgianos PI, Bakris GL. Advances in treatment of hyperkalemia in chronic kidney disease. *Expert Opin Pharmacother* 2015; 16: 2205–2215.
  55. Fried LF, Duckworth W, Zhang JH et al. Design of combination angiotensin receptor blocker and angiotensin-converting enzyme inhibitor for treatment of diabetic nephropathy (VA NEPHRON-D). *Clin J Am Soc Nephrol* 2009; 4: 361–368.
  56. Hollenberg NK. Aldosterone in the development and progression of renal injury. *Kidney Int* 2004; 66: 1–9.
  57. Bakris GL, Siomos M, Richardson D et al. ACE inhibition or angiotensin receptor blockade: Impact on potassium in renal failure. VAL-K Study Group. *Kidney Int* 2000; 58: 2084–2092.
  58. Chrysostomou A, Pedagogos E, MacGregor L, Becker GJ. Double-blind, placebo-controlled study on the effect of the aldosterone receptor antagonist spironolactone in patients who have persistent proteinuria and are on long-term angiotensin-converting enzyme inhibitor therapy, with or without an angiotensin II receptor blocker. *Clin J Am Soc Nephrol* 2006; 1: 256–262.
  59. Rossing K, Schjoedt KJ, Smidt UM et al. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy: A randomized, double-masked, crossover study. *Diabetes Care* 2005; 28: 2106–2112.
  60. Schjoedt KJ, Rossing K, Juhl TR et al. Beneficial impact of spironolactone in diabetic nephropathy. *Kidney Int* 2005; 68: 2829–2836.
  61. Schjoedt KJ, Rossing K, Juhl TR et al. Beneficial impact of spironolactone on nephrotic range albuminuria in diabetic nephropathy. *Kidney Int* 2006; 70: 536–542.
  62. Sarafidis PA, Blacklock R, Wood E et al. Prevalence and factors associated with hyperkalemia in predialysis patients followed in a low-clearance clinic. *Clin J Am Soc Nephrol* 2012; 7: 1234–1241.
  63. Sarafidis PA, Georgianos PI, Lasaridis AN. Diuretics in clinical practice. Part II: Electrolyte and acid-base disorders complicating diuretic therapy. *Expert Opin Drug Saf* 2010; 9: 259–273.
  64. Pitt B, Reichel N, Willenbrock R et al. Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: The 4E-left ventricular hypertrophy study. *Circulation* 2003; 108: 1831–1838.
  65. Bakris GL, Agarwal R, Chan JC et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy: A randomized clinical trial. *JAMA* 2015; 314: 884–894.

66. Bakris GL, Copley JB, Vicknair N et al. Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. *Kidney Int* 1996; 50: 1641–1650.
67. Bakris GL, Mangrum A, Copley JB et al. Effect of calcium channel or beta-blockade on the progression of diabetic nephropathy in African Americans. *Hypertension* 1997; 29: 744–750.
68. Smith AC, Toto R, Bakris GL. Differential effects of calcium channel blockers on size selectivity of proteinuria in diabetic glomerulopathy. *Kidney Int* 1998; 54: 889–896.
69. Griffin KA, Picken MM, Bakris GL, Bidani AK. Class differences in the effects of calcium channel blockers in the rat remnant kidney model. *Kidney Int* 1999; 55: 1849–1860.
70. Adler AI, Stratton IM, Neil HA et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): Prospective observational study. *BMJ* 2000; 321: 412–419.
71. Ruggenenti P, Perna A, Loriga G et al. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): Multicentre, randomised controlled trial. *Lancet* 2005; 365: 939–946.
72. Rahman M, Pressel S, Davis BR et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: A report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2005; 165: 936–946.
73. Bakris GL, Sarafidis PA, Weir MR et al. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): A prespecified secondary analysis of a randomised controlled trial. *Lancet* 2010; 375: 1173–1181.
74. Sarafidis PA, Georgianos P, Bakris GL. Resistant hypertension—its identification and epidemiology. *Nat Rev Nephrol* 2013; 9: 51–58.
75. Slagman MC, Waanders F, Hemmelder MH et al. Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: Randomised controlled trial. *BMJ* 2011; 343: d4366.
76. Vegter S, Perna A, Postma MJ et al. Sodium intake, ACE inhibition, and progression to ESRD. *J Am Soc Nephrol* 2012; 23: 165–173.
77. Sarafidis PA, Georgianos PI, Lasaridis AN. Diuretics in clinical practice. Part I: Mechanisms of action, pharmacological effects and clinical indications of diuretic compounds. *Expert Opin Drug Saf* 2010; 9: 243–257.
78. Bakris GL, Smith A. Effects of sodium intake on albumin excretion in patients with diabetic nephropathy treated with long-acting calcium antagonists. *Ann Intern Med* 1996; 125: 201–204.
79. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. *BMJ* 1998; 317: 713–720.
80. Bakris GL, Fonseca V, Katholi RE et al. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: A randomized controlled trial. *JAMA* 2004; 292: 2227–2236.
81. Hannedouche T, Roth H, Krummel T et al. Multiphasic effects of blood pressure on survival in hemodialysis patients. *Kidney Int* 2016; 90: 674–684.
82. Mazzuchi N, Carbonell E, Fernandez-Cean J. Importance of blood pressure control in hemodialysis patient survival. *Kidney Int* 2000; 58: 2147–2154.
83. Parati G, Ochoa JE, Bilo G et al. Hypertension in chronic kidney disease part 2: Role of ambulatory and home blood pressure monitoring for assessing alterations in blood pressure variability and blood pressure profiles. *Hypertension* 2016; 67: 1102–1110.
84. Parati G, Ochoa JE, Bilo G et al. Hypertension in chronic kidney disease part 1: Out-of-office blood pressure monitoring: Methods, thresholds, and patterns. *Hypertension* 2016; 67: 1093–1101.
85. Zoccali C, Tripepi R, Torino C et al. Moderator's view: Ambulatory blood pressure monitoring and home blood pressure for the prognosis, diagnosis and treatment of hypertension in dialysis patients. *Nephrol Dial Transplant* 2015; 30: 1443–1448.
86. Sarafidis PA, Persu A, Agarwal R et al. Hypertension in dialysis patients: A consensus document by the European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) and the Hypertension and the Kidney working group of the European Society of Hypertension (ESH). *J Hypertens* 2017; 35: 657–676.
87. Georgianos PI, Sarafidis PA. Pro: Should we move to more frequent haemodialysis schedules? *Nephrol Dial Transplant* 2015; 30: 18–22.
88. Karpetas A, Loutradis C, Bikos A et al. Blood pressure variability is increasing from the first to the second day of the interdialytic interval in hemodialysis patients. *J Hypertens* 2017; 35: 2517–2526.
89. Georgianos PI, Sarafidis PA, Zoccali C. Intradialysis hypertension in end-stage renal disease patients: Clinical epidemiology, pathogenesis, and treatment. *Hypertension* 2015; 66: 456–463.
90. Agarwal R, Brim NJ, Mahenthiran J et al. Out-of-hemodialysis-unit blood pressure is a superior determinant of left ventricular hypertrophy. *Hypertension* 2006; 47: 62–68.
91. Alborzi P, Patel N, Agarwal R. Home blood pressures are of greater prognostic value than hemodialysis unit recordings. *Clin J Am Soc Nephrol* 2007; 2: 1228–1234.
92. Agarwal R. Blood pressure and mortality among hemodialysis patients. *Hypertension* 2010; 55: 762–768.
93. Zoccali C, Benedetto FA, Tripepi G et al. Nocturnal hypoxemia, night-day arterial pressure changes and left ventricular geometry in dialysis patients. *Kidney Int* 1998; 53: 1078–1084.
94. Tripepi G, Fagugli RM, Datolo P et al. Prognostic value of 24-hour ambulatory blood pressure monitoring and of night/day ratio in nondiabetic, cardiovascular events-free hemodialysis patients. *Kidney Int* 2005; 68: 1294–1302.
95. Agarwal R. Pro: Ambulatory blood pressure should be used in all patients on hemodialysis. *Nephrol Dial Transplant* 2015; 30: 1432–1437.
96. Sarafidis PA, Rumjon A, Macdougall IC. Ambulatory blood pressure monitoring: An invaluable tool comes of age for patients with chronic kidney disease? *Am J Nephrol* 2012; 35: 238–241.
97. Salem MM, Bower J. Hypertension in the hemodialysis population: Any relation to one-year survival? *Am J Kidney Dis* 1996; 28: 737–740.
98. Rahman M, Dixit A, Donley V et al. Factors associated with inadequate blood pressure control in hypertensive hemodialysis patients. *Am J Kidney Dis* 1999; 33: 498–506.
99. Agarwal R, Nissenson AR, Battle D et al. Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States. *Am J Med* 2003; 115: 291–297.
100. Agarwal R. Epidemiology of interdialytic ambulatory hypertension and the role of volume excess. *Am J Nephrol* 2011; 34: 381–390.
101. Loutradis C, Karpetas A, Piperidou A et al. Prevalence and control of hypertension with the use of ambulatory blood pressure recording in hemodialysis patients. *Arterial Hypertens* 2017; 26: 205–214.
102. Cocchi R, Degli Esposti E, Fabbri A et al. Prevalence of hypertension in patients on peritoneal dialysis: Results of an Italian multicentre study. *Nephrol Dial Transplant* 1999; 14: 1536–1540.
103. Agarwal R, Flynn J, Pogue V et al. Assessment and management of hypertension in patients on dialysis. *J Am Soc Nephrol* 2014; 25: 1630–1646.
104. Atas N, Erten Y, Okay GU et al. Left ventricular hypertrophy and blood pressure control in automated and continuous ambulatory peritoneal dialysis patients. *Ther Apher Dial* 2014; 18: 297–304.
105. Nossens TT, Konings CJ, Fagel WJ et al. Fluid state and blood pressure control: No differences between APD and CAPD. *Asaio J* 2012; 58: 132–136.
106. Enia G, Mallamaci F, Benedetto FA et al. Long-term CAPD patients are volume expanded and display more severe left ventricular hypertrophy than haemodialysis patients. *Nephrol Dial Transplant* 2001; 16: 1459–1464.
107. Tonbul Z, Altintepe L, Sozlu C et al. Ambulatory blood pressure monitoring in haemodialysis and continuous ambulatory peritoneal dialysis (CAPD) patients. *J Hum Hypertens* 2002; 16: 585–589.
108. Rodby RA, Vonesh EF, Korbet SM. Blood pressures in hemodialysis and peritoneal dialysis using ambulatory blood pressure monitoring. *Am J Kidney Dis* 1994; 23: 401–411.
109. Locatelli F, Covic A, Chazot C et al. Hypertension and cardiovascular risk assessment in dialysis patients. *Nephrol Dial Transplant* 2004; 19: 1058–1068.
110. Karpetas A, Sarafidis PA, Georgianos PI et al. Ambulatory recording of wave reflections and arterial stiffness during intra- and interdialytic periods in patients treated with dialysis. *Clin J Am Soc Nephrol* 2015; 10: 630–638.
111. Kelley K, Light RP, Agarwal R. Trended cosinor change model for analyzing hemodynamic rhythm patterns in hemodialysis patients. *Hypertension* 2007; 50: 143–150.



112. Koutroumbas G, Georgianos PI, Sarafidis PA et al. Ambulatory aortic blood pressure, wave reflections and pulse wave velocity are elevated during the third in comparison to the second interdialytic day of the long interval in chronic haemodialysis patients. *Nephrol Dial Transplant* 2015; 30: 2046–2053.
113. Georgianos PI, Sarafidis PA, Haidich AB et al. Diverse effects of interdialytic intervals on central wave augmentation in haemodialysis patients. *Nephrol Dial Transplant* 2013; 28: 2160–2169.
114. Converse RL, Jr., Jacobsen TN, Toto RD et al. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 1992; 327: 1912–1918.
115. Hausberg M, Kosch M, Harmelink P et al. Sympathetic nerve activity in end-stage renal disease. *Circulation* 2002; 106: 1974–1979.
116. Ott C, Schmid A, Ditting T et al. Renal denervation in a hypertensive patient with end-stage renal disease and small arteries: A direction for future research. *J Clin Hypertens (Greenwich)* 2012; 14: 799–801.
117. Papademetriou V, Doumas M, Anyfanti P et al. Renal nerve ablation for hypertensive patients with chronic kidney disease. *Curr Vasc Pharmacol* 2014; 12: 47–54.
118. Bazzato G, Coli U, Landini S et al. Prevention of intra- and post-dialytic hypertensive crises by captopril. *Contrib Nephrol* 1984; 41: 292–298.
119. Henrich WL, Katz FH, Molinoff PB, Schrier RW. Competitive effects of hypokalemia and volume depletion on plasma renin activity, aldosterone and catecholamine concentrations in hemodialysis patients. *Kidney Int* 1977; 12: 279–284.
120. Georgianos PI, Sarafidis PA, Lasaridis AN. Arterial stiffness: A novel cardiovascular risk factor in kidney disease patients. *Curr Vasc Pharmacol* 2015; 13: 229–238.
121. Sarafidis PA, Loutradis C, Karpeta A et al. Ambulatory pulse wave velocity is a stronger predictor of cardiovascular events and all-cause mortality than office and ambulatory blood pressure in hemodialysis patients. *Hypertension* 2017; 70: 148–157.
122. Agarwal R, Light RP. Arterial stiffness and interdialytic weight gain influence ambulatory blood pressure patterns in hemodialysis patients. *Am J Physiol Renal Physiol* 2008; 294: F303–F308.
123. Morris ST, McMurray JJ, Spiers A, Jardine AG. Impaired endothelial function in isolated human uremic resistance arteries. *Kidney Int* 2001; 60: 1077–1082.
124. Raptis V, Kapoulas S, Grekas D. Role of asymmetrical dimethyl-arginine in the progression of renal disease. *Nephrology (Carlton)* 2013; 18: 11–21.
125. Ok E, Asci G, Chazot C et al. Controversies and problems of volume control and hypertension in haemodialysis. *Lancet* 2016; 388: 285–293.
126. Katzarski KS, Charra B, Luik AJ et al. Fluid state and blood pressure control in patients treated with long and short haemodialysis. *Nephrol Dial Transplant* 1999; 14: 369–375.
127. Laurent G, Charra B. The results of an 8 h thrice weekly haemodialysis schedule. *Nephrol Dial Transplant* 1998; 13(Suppl 6): 125–131.
128. Agarwal R, Alborzi P, Satyan S, Light RP. Dry-weight reduction in hypertensive hemodialysis patients (DRIP): A randomized, controlled trial. *Hypertension* 2009; 53: 500–507.
129. Kayikcioglu M, Tumuklu M, Ozkahya M et al. The benefit of salt restriction in the treatment of end-stage renal disease by haemodialysis. *Nephrol Dial Transplant* 2009; 24: 956–962.
130. Inrig JK. Intradialytic hypertension: A less-recognized cardiovascular complication of hemodialysis. *Am J Kidney Dis* 2010; 55: 580–589.
131. Torino C, Gargani L, Sicari R et al. The agreement between auscultation and lung ultrasound in hemodialysis patients: The LUST study. *Clin J Am Soc Nephrol* 2016; 11: 2005–2011.
132. Zhu F, Rosales L, Kotanko P. Techniques for assessing fluids status in patients with kidney disease. *Curr Opin Nephrol Hypertens* 2016; 25: 473–479.
133. Zoccali C, Puntorieri E, Mallamaci F. Lung congestion as a hidden threat in end-stage kidney disease: A call to action. *Nephrol Dial Transplant* 2013; 28: 2657–2660.
134. Loutradis CN, Tsioufis C, Sarafidis PA. The clinical problems of hypertension treatment in hemodialysis patients. *Curr Vasc Pharmacol* 2017; 16: 54–60.
135. Hecking M, Karaboyas A, Antlanger M et al. Significance of interdialytic weight gain versus chronic volume overload: Consensus opinion. *Am J Nephrol* 2013; 38: 78–90.
136. Ozkahya M, Toz H, Qzerkan F et al. Impact of volume control on left ventricular hypertrophy in dialysis patients. *J Nephrol* 2002; 15: 655–660.
137. Song JH, Lee SW, Suh CK, Kim MJ. Time-averaged concentration of dialysate sodium relates with sodium load and interdialytic weight gain during sodium-profiling hemodialysis. *Am J Kidney Dis* 2002; 40: 291–301.
138. Manlucu J, Gallo K, Heidenheim PA, Lindsay RM. Lowering postdialysis plasma sodium (conductivity) to increase sodium removal in volume-expanded hemodialysis patients: A pilot study using a biofeedback software system. *Am J Kidney Dis* 2010; 56: 69–76.
139. Weiner DE, Brunelli SM, Hunt A et al. Improving clinical outcomes among hemodialysis patients: A proposal for a ‘volume first’ approach from the chief medical officers of US dialysis providers. *Am J Kidney Dis* 2014; 64: 685–695.
140. Rahman M, Fu P, Sehgal AR, Smith MC. Interdialytic weight gain, compliance with dialysis regimen, and age are independent predictors of blood pressure in hemodialysis patients. *Am J Kidney Dis* 2000; 35: 257–265.
141. Georgianos PI, Sarafidis PA, Sinha AD, Agarwal R. Adverse effects of conventional thrice-weekly hemodialysis: Is it time to avoid 3-day interdialytic intervals? *Am J Nephrol* 2015; 41: 400–408.
142. Chertow GM, Levin NW, Beck GJ et al. In-center hemodialysis six times per week versus three times per week. *N Engl J Med* 2010; 363: 2287–2300.
143. Ok E, Duman S, Asci G et al. Comparison of 4- and 8-h dialysis sessions in thrice-weekly in-centre haemodialysis: A prospective, case-controlled study. *Nephrol Dial Transplant* 2011; 26: 1287–1296.
144. Kotanko P, Garg AX, Depner T et al. Effects of frequent hemodialysis on blood pressure: Results from the randomized frequent hemodialysis network trials. *Hemodial Int* 2015; 19: 386–401.
145. Chertow GM, Levin NW, Beck GJ et al. Long-term effects of frequent in-center hemodialysis. *J Am Soc Nephrol* 2016; 27: 1830–1836.
146. Rocco MV, Daugirdas JT, Greene T et al. Long-term effects of frequent nocturnal hemodialysis on mortality: The frequent hemodialysis network (FHN) nocturnal trial. *Am J Kidney Dis* 2015; 66: 459–468.
147. Daugirdas JT, Greene T, Rocco MV et al. Effect of frequent hemodialysis on residual kidney function. *Kidney Int* 2013; 83: 949–958.
148. Inrig JK. Antihypertensive agents in hemodialysis patients: A current perspective. *Semin Dial* 2010; 23: 290–297.
149. Levin NW, Kotanko P, Eckardt KU et al. Blood pressure in chronic kidney disease stage 5D-report from a Kidney Disease: Improving Global Outcomes Controversies Conference. *Kidney Int* 2010; 77: 273–284.
150. Agarwal R, Sinha AD. Cardiovascular protection with antihypertensive drugs in dialysis patients: Systematic review and meta-analysis. *Hypertension* 2009; 53: 860–866.
151. Heerspink HJ, Ninomiya T, Zoungas S et al. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: A systematic review and meta-analysis of randomised controlled trials. *Lancet* 2009; 373: 1009–1015.
152. Zannad F, Kessler M, Leheret P et al. Prevention of cardiovascular events in end-stage renal disease: Results of a randomized trial of foscipril and implications for future studies. *Kidney Int* 2006; 70: 1318–1324.
153. Zoccali C, Mallamaci F. Pleiotropic effects of angiotensin II blockers in hemodialysis patients: Myth or reality? *Kidney Int* 2014; 86: 469–471.
154. Takahashi A, Takase H, Toriyama T et al. An angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients on chronic haemodialysis—a randomized study. *Nephrol Dial Transplant* 2006; 21: 2507–2512.
155. Suzuki H, Kanno Y, Sugahara S et al. Effect of angiotensin receptor blockers on cardiovascular events in patients undergoing hemodialysis: An open-label randomized controlled trial. *Am J Kidney Dis* 2008; 52: 501–506.
156. Iseki K, Arima H, Kohagura K et al. Effects of angiotensin receptor blockade (ARB) on mortality and cardiovascular outcomes in patients with long-term haemodialysis: A randomized controlled trial. *Nephrol Dial Transplant* 2013; 28: 1579–1589.
157. Ni X, Zhang J, Zhang P et al. Effects of spironolactone on dialysis patients with refractory hypertension: A randomized controlled study. *J Clin Hypertens (Greenwich)* 2014; 16: 658–663.
158. Matsumoto Y, Mori Y, Kageyama S et al. Spironolactone reduces cardiovascular and cerebrovascular morbidity and mortality in hemodialysis patients. *J Am Coll Cardiol* 2014; 63: 528–536.
159. Lin C, Zhang Q, Zhang H, Lin A. Long-term effects of low-dose spironolactone on chronic dialysis patients: A randomized

- placebo-controlled study. *J Clin Hypertens (Greenwich)* 2016; 18: 121–128.
160. Denker MG, Cohen DL. Antihypertensive medications in end-stage renal disease. *Semin Dial* 2015; 28: 330–336.
  161. Cice G, Ferrara L, D'Andrea A et al. Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: A prospective, placebo-controlled trial. *J Am Coll Cardiol* 2003; 41: 1438–1444.
  162. Agarwal R, Sinha AD, Pappas MK et al. Hypertension in hemodialysis patients treated with atenolol or lisinopril: A randomized controlled trial. *Nephrol Dial Transplant* 2014; 29: 672–681.
  163. Weir MA, Dixon SN, Fleet JL et al. Beta-Blocker dialyzability and mortality in older patients receiving hemodialysis. *J Am Soc Nephrol* 2015; 26: 987–996.
  164. London GM, Marchais SJ, Guerin AP et al. Salt and water retention and calcium blockade in uremia. *Circulation* 1990; 82: 105–113.
  165. Tepel M, Hopfenmueller W, Scholze A et al. Effect of amlodipine on cardiovascular events in hypertensive haemodialysis patients. *Nephrol Dial Transplant* 2008; 23: 3605–3612.



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# BLOOD PRESSURE MANAGEMENT IN ACUTE STROKE

# 58

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## INTRODUCTION

Arterial hypertension is one of the most important modifiable risk factors for stroke. Several observational studies have revealed a positive and continuous association between blood pressure (BP) levels and stroke (1). Furthermore, primary and secondary prevention clinical trials have demonstrated that BP reduction diminishes the risk of first-ever and recurrent stroke, respectively, independent of baseline BP levels. However, during the acute phase of stroke, the optimal management of arterial hypertension remains an issue of longstanding debate and of little consensus, since the results of the observational studies are conflicting, and the findings of the randomized clinical trials (RCTs) are neutral.

Arterial hypertension is common during the acute stage of stroke. Raised BP values ( $>140/90$  mmHg) are present in up to 80% of patients with acute stroke, while almost 25% of them present with markedly elevated systolic blood pressure (SBP) values ( $>180$  mmHg) (2). Increased BP levels at the acute phase of stroke are mainly associated with pre-existing hypertension, activation of neuroendocrine systems, stress of hospitalization, infarct topography, stroke subtype, stroke severity and the reactive elevations of systematic BP in response to raised intracranial pressure (Cushing reflex).

## ISCHAEMIC STROKE

Based on pathophysiological facts and research findings, the management of post-stroke hypertension remains controversial since there are arguments against and in favour of BP lowering during the acute phase of stroke.

On the one hand, BP reduction in acute stroke patients should be avoided because:

- BP tends to normalize spontaneously within hours or days after ischaemic stroke (IS) onset (3).
- The cerebral autoregulation (which maintains cerebral perfusion over a wide range of systematic BP) becomes dysfunctional during the acute stage of stroke and

cerebral perfusion tends to be passively dependent on systematic BP. Hence, active BP lowering may cause a decrease of cerebral blood flow in the area of the ischaemic penumbra resulting in infarct extension and worsening of outcome. The former hypothesis has been supported by the findings of the Nimodipine West European Trial, which reported that intensive BP lowering (DBP drop  $>20\%$ ) using high-dose intravenous nimodipine was associated with neurological worsening in acute stroke patients (4).

- Several observational studies have demonstrated a U-shaped relationship between acute BP levels and IS outcome. Both high and low BP values were independent prognostic factors for unfavourable outcome. Low BP values (SBP  $<120$  mmHg) during the acute phase of stroke have been associated with higher stroke severity (total anterior circulation syndrome) and increased mortality due to coronary heart disease (5,6).

On the other hand, there is evidence that moderate BP lowering might be beneficial in the acute stroke setting because:

- Sustained high ambulatory BP values have been associated with subsequent oedema formation (7).
- Based on the above-mentioned U-shaped relationship between admission BP values and IS outcome, the unfavourable outcome among acute stroke patients with elevated BP values seems to be attributed to the higher rates of early and late stroke recurrence, cerebral oedema and mortality due to oedema formation (5,6).

## RANDOMIZED CLINICAL TRIALS

Several RCTs evaluated the impact of treatment-induced BP lowering on outcome in acute IS patients (Table 58.1). However, almost all trials failed to demonstrate that active antihypertensive treatment and BP lowering improve outcome in the setting of acute IS.

**Table 58.1** Randomized clinical trials: blood pressure management and outcome in acute ischaemic stroke

| Study        | n    | Drug                                         | Inclusion BP                                                                                                                                      | Mean BP reduction                                                                                                                  | Outcome                                                                                                                                                                        |
|--------------|------|----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ACCESS (8)   | 342  | Candesartan                                  | Mean SBP 6–24 h after admission $\geq 200$ mmHg or DBP $\geq 110$ mmHg<br>Mean SBP 24–36 h after admission $\geq 180$ mmHg or DBP $\geq 105$ mmHg | No significant reduction                                                                                                           | No difference in Barthel Index at 3 months. No difference in cerebrovascular events at 12 months. Reduced mortality and vascular events at 12 months in favour of candesartan. |
| SCAST (9)    | 2029 | Candesartan                                  | SBP $> 140$ mmHg.<br>Fixed dose-escalation schedule                                                                                               | $\downarrow$ SBP 5 mmHg and $\downarrow$ DBP 2 mmHg on day 7                                                                       | No difference in mRS or stroke recurrence at 6 months.                                                                                                                         |
| CHHIPS (11)  | 179  | Oral labetalol or lisinopril or placebo      | SBP $> 160$ mmHg                                                                                                                                  | $\downarrow$ SBP 14 mmHg and $\downarrow$ DBP 7 mmHg with lisinopril at 24 hours                                                   | No difference in death or dependency rate at 2 weeks.                                                                                                                          |
| COSSACS (12) | 763  | Continuation of home medications             | SBP $< 200$ mmHg and DBP $< 120$ mmHg                                                                                                             | $\downarrow$ SBP 13 mmHg and $\downarrow$ DBP 8 mmHg at 2 weeks                                                                    | No difference in death or dependency rate at 2 weeks. No difference in stroke recurrence at 6 months.                                                                          |
| CATIS (13)   | 4071 | ACE-I, CCB, diuretics (predefined algorithm) | SBP of 140–200 mmHg                                                                                                                               | $\downarrow$ SBP 8.1 mmHg and $\downarrow$ DBP 3.8 mmHg at 24 h, $\downarrow$ SBP 9.3 mmHg and $\downarrow$ DBP 4.0 mmHg at 7 days | No difference in death or disability rate at 14 days after randomization. No difference in mRS at 3 months.                                                                    |
| ENOS (14)    | 4011 | Glyceryl trinitrate (transdermal)            | SBP of 140–220 mmHg                                                                                                                               | $\downarrow$ SBP 7.0 mmHg and $\downarrow$ DBP 3.5 mmHg at 24 h, $\downarrow$ SBP 9.5 mmHg and $\downarrow$ DBP 5.0 mmHg on day 7  | Significant BP lowering, acceptable safety but not improvement in functional outcome                                                                                           |

Abbreviations: n, number of patients; h, hours; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; mRS, modified Rankin scale; ACE-I, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker.

In the ACCESS study (Acute Candesartan Cilexetil Therapy in Stroke Survivors), 339 patients with acute IS and BP values greater than 180/105 mmHg were randomized to oral candesartan or placebo within 36 hours after admission and maintained on study drug for 7 days after randomization (8). The two groups did not differ regarding functional outcome and risk of stroke recurrence at 3 and 12 months, respectively. However, candesartan significantly reduced mortality and vascular events during the 12-month follow-up. The superiority of candesartan versus placebo over the secondary endpoint of the study triggered the design of a larger study. In the SCAST study (Scandinavian Candesartan Acute Stroke Trial), a phase III RCT, 2029 patients with acute IS (85%) or ICH (15%) and SBP ( $> 140$  mmHg) were randomized to oral candesartan or placebo using a design similar to ACCESS (9). The composite endpoint of major cardiovascular events did not differ between the two groups at 6 months. However, patients treated with candesartan had a worse functional outcome compared to those receiving placebo. In addition, a SCAST substudy showed that in patients with moderate to severe carotid artery disease treated with candesartan, progressive stroke occurred more frequently than in the placebo group (10).

Two more studies investigating the same research question in the United Kingdom have reported similar results. The CHHIPS (Randomized Stroke and Stroke Hypotension) study randomized 179 patients with ischaemic (85%) or haemorrhagic stroke (15%) and SBP ( $> 160$  mmHg) within

36 hours of symptoms onset to labetalol, lisinopril or placebo (11). There were no differences in the primary endpoint of 14-day death, dependency, early neurological deterioration and serious adverse events. However, 3-month mortality showed a trend favouring active treatment. This preliminary observation remains to be confirmed by a larger phase III trial. In the COSSACS (Continue or Stop Post-Stroke Antihypertensives Collaborative Study) study, 763 patients with ischaemic (95%) or haemorrhagic stroke (5%) were randomized to continue or to stop their antihypertensive treatment prior to stroke onset (12). The continuation of previously administered antihypertensive treatment in acute stroke patients was not associated with improved mortality or disability at 2 weeks and 6 months of follow-up.

The most recently published studies were the CATIS and ENOS trials. The CATIS (China Antihypertensive Trial in Acute Ischaemic Stroke) study included 4071 patients with IS within 48 hours of symptom onset and SBP levels of 140–220 mmHg (13). Patients were randomized to an SBP reduction target of 10–25% within 24 hours of randomization and a BP of  $< 140/90$  mmHg within 7 days with the use of agents of angiotensin-converting enzyme inhibitors, calcium channel blockers and diuretics according to a predefined algorithm versus no antihypertensive treatment. The two groups did not differ regarding the primary composite endpoint of death and dependency rate at 14 days and the secondary endpoint of functional disability at 3 months. However, when antihypertensive therapy was



started >24 hours of symptoms onset there was a significant reduction of the primary endpoint in the treatment group.

Finally, in ENOS (Efficacy of Nitric Oxide in Stroke) trial, 4011 patients with ischaemic or haemorrhagic stroke and SBP (140–220 mmHg) were allocated to treatment with transdermal glyceryl trinitrate or placebo within 48 hours of stroke onset and for 7 days (14). The administration of glyceryl trinitrate did not improve functional outcome at 3 months compared with placebo. In contrast to the CATIS trial, a prespecified subgroup analysis of ENOS demonstrated that the early onset of active therapy, within 6 hours of ictus, was associated with a favourable functional outcome and fewer deaths. Thus, the optimal timing of antihypertensive therapy initiation during the acute phase of IS remains controversial.

The U-shaped relationship between baseline BP values and outcome revealed that both markedly elevated and low BP values (<120 mmHg) are associated with poor outcome. Thus it could be theoretically assumed that raising BP might be beneficial in selected patients. Studies in animal models have demonstrated that the administration of phenylephrine after stroke improved cerebral blood flow and reduced cerebral oedema in the territory of the infarction. Unfortunately, no RCTs have evaluated the safety and efficacy of treatment-induced hypertension in the setting of acute ischaemic stroke. The available evidence derived from retrospective and small randomized studies suggests that raising BP up to 20% with intravenously administered phenylephrine in selected acute IS patients is safe and may be associated with neurological improvement. The best studied candidates for induced hypertension are those with large perfusion deficits caused by steno-occlusive disease who are not eligible for thrombolytic or interventional treatments.

Despite several published RCTs, the optimal BP management in acute IS patients is still unclear. The neutral results of all trials regarding the effect of BP lowering on death and dependency in the setting of acute stroke demonstrate that either reducing BP is not of benefit or the study designs were inappropriate to reveal positive associations between BP modulation and outcome. Stroke is a complex disease and the 'one size fits all' approach in terms of BP lowering in IS may not be valid. Future studies should take into account IS subtypes (separate evaluation of large and small vessel disease strokes), timing of administration (early administration <24 h), route of therapeutic manipulation (intravenously, easily titrated agents), recruitment of patients with higher SBP values (>160 mmHg) and targeting greater SBP goals (<150 mmHg). These trials may provide adequate scientific basis for more evidence-based treatment decisions regarding BP management in acute IS patients.

## BLOOD PRESSURE MANAGEMENT IN PATIENTS ELIGIBLE FOR THROMBOLYSIS

Although a significant proportion of patients with acute IS are treated with intravenous thrombolysis, there are no data from RCTs demonstrating the relationship between BP levels and outcome in these patients. Current guidelines regarding BP management in acute IS patients eligible for thrombolysis are based mainly on expert

consensus, extrapolating the findings from thrombolysis trials in the setting of myocardial infarction. The most important observational study supporting the association of high BP values and adverse outcome in patients with acute IS treated with intravenous thrombolysis is the SITS-ISTR (Safe Implementation of Thrombolysis in Stroke – International Stroke Thrombolysis Register) study (15). This study showed that BP levels during the first 24 hours following intravenous thrombolysis were positively and linearly associated with the risk of intracerebral haemorrhage. Moreover, during the first 24 hours post-thrombolysis, a U-shaped relationship was observed between BP values and mortality and disability. An SBP of 141–150 mmHg was associated with the more favourable outcome.

## INTRACEREBRAL HAEMORRHAGE

Similar to acute IS, the optimal management of post-stroke hypertension in patients with intracerebral haemorrhage (ICH) is still uncertain. Although elevated BP declines spontaneously within the first days after ICH onset and aggressive BP reduction may decrease cerebral perfusion pressure in the area surrounding haematoma leading to neurological worsening, most arguments are in favour of BP lowering. Observational studies have illustrated that elevated BP is associated with increased risk of death, disability or neurological deterioration in patients with acute haemorrhagic stroke (6,16). In addition, some studies have demonstrated that increased BP is related to haematoma growth and to cerebral oedema formation (7,17). Haematoma expansion is a frequent complication of ICH, occurring in 30% of patients with haemorrhagic stroke, whilst one-third of them develop the expansion within 3 hours of ICH (18). Several studies have reported that haematoma enlargement is associated with neurological deterioration and poor outcome (19,20). Haematoma volumes greater than 30 mL are related to increased mortality rates (60–90%) at 1 month after ICH (21). Of note, the INTERACT1 study revealed that for each 1-mL increase in haematoma expansion, the risk of death and dependency increases by 5% (22). Hence this has prompted some researchers to conclude that haematoma growth might be the biological link between elevated BP and mortality. The possible beneficial effects of early BP-lowering treatment on haematoma enlargement and outcome after ICH have led to the conduction of RCTs aiming to determine the safety and efficacy of early BP management on haematoma expansion and hard outcomes such as mortality and disability (Table 58.2).

## RANDOMIZED CLINICAL TRIALS

The safety of intensive BP-lowering treatment in patients with acute haemorrhagic stroke was investigated by two pilot, prospective, randomized trials, which were used as feasibility studies allowing the designing of larger trials. The INTERACT1 (INTensive blood pressure Reduction in Acute Cerebral haemorrhage Trial), an international, open-label, blinded endpoint trial, enrolled 404 patients with acute ICH and elevated SBP levels (150–220 mmHg)

**Table 58.2** Randomized clinical trials: Blood pressure management and outcome in acute intracerebral haemorrhage

| Study           | n    | Inclusion BP                                                   | Target BP                                                                                                         | Outcome                                                                                                                                                                     |
|-----------------|------|----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| INTERACT-1 (23) | 404  | <6 h since onset, SBP (150–220) mmHg                           | 140 mmHg vs. 180 mmHg                                                                                             | Reduction in haematoma growth at 24 h                                                                                                                                       |
| ICH-ADAPT (26)  | 75   | <24 h since onset, SBP >150 mmHg                               | 150 mmHg vs. 180 mmHg                                                                                             | No significant difference in perihematoma CBF                                                                                                                               |
| ATACH-1 (24)    | 60   | <6 h since onset, SBP ≥170 mmHg                                | 170–200 mmHg in the first cohort of patients; 140–170 mmHg in the second cohort; 110–140 mmHg in the third cohort | Neurologic deterioration and serious adverse events were below the prespecified safety thresholds, and the 3-month mortality rate was lower than expected in all SBP tiers. |
| INTERACT-2 (28) | 2794 | <6 h since onset, SBP (150–220) mmHg                           | 140 mmHg vs. 180 mmHg                                                                                             | No significant reduction in the rate death or severe disability. Improved functional outcomes (ordinal analysis of mRS) with intensive lowering of blood pressure.          |
| ATACH-2 (29)    | 1000 | 3 and 4.5 h since onset, at least one reading of SBP ≥180 mmHg | <140 (110–139) mmHg vs. 140–179 mmHg                                                                              | Not lower rate of death or disability. Significantly higher rates of renal adverse events at 7 days in the aggressive BP-lowering group.                                    |

Abbreviations: n, number of patients; h, hours; BP, blood pressure; SBP, systolic blood pressure; CBF, cerebral blood flow; mRS, modified Rankin Scale.

within 6 hours of ICH onset and randomized them to either intensive BP treatment (SBP target <140 mmHg within 1 hour of randomization and maintaining it for the next 7 days) or guideline-based management of BP (SBP target <180 mmHg) (23). The choice of antihypertensive treatment was determined by the investigator's preference. The aim of the study was to assess safety, efficacy (proportional change in haematoma volume at 24 hours) and clinical outcomes (death or disability) of treatment at 90 days. The rates of serious adverse events, neurological deterioration and poor clinical outcome did not differ significantly between the two groups. Furthermore, intensive BP reduction attenuated proportional haematoma growth at 24 hours, not significantly though.

In the prospective, open-label, ATACH1 (Antihypertensive Treatment of Acute Cerebral Haemorrhage) study, 60 patients with acute haemorrhagic stroke and SBP >170 mmHg were randomized, within 6 hours of symptom onset, into one of three SBP target levels: 170–199, 140–169 and 110–139 mmHg (24). Patients were treated with intravenous nicardipine for achieving and maintaining BP goals for 24 hours. The study aimed to determine feasibility, safety (neurological deterioration at 24 hours and serious adverse events at 72 hours) and efficacy (disability or death at 90 days) of intensive BP reduction. The mortality at 3 months was lower than expected across all SBP levels and the rates of serious adverse events and neurological deterioration were below the prespecified safety thresholds. A post hoc analysis of ATACH1 trial did not reveal any significant associations between different SBP levels and haematoma expansion (25).

Both pilot trials demonstrated that intensive BP lowering in the setting of acute ICH is safe and feasible and may be associated with reduced haematoma growth. However, the opponents of this treatment strategy are concerned that the already compromised cerebral blood flow (CBF) in the perihematoma area due to the compression of small arteries by the haematoma and the associated oedema will be further reduced by aggressive BP lowering, leading subsequently to perihematoma ischaemia. The ICH-ADAPT

(Intracerebral Haemorrhage Acutely Decreasing Arterial Pressure Trial) assessed the impact of aggressive BP lowering on CBF and provided strong arguments against this hazard (26). A total of 75 patients with acute haemorrhagic stroke and SBP >150 mmHg were randomly assigned within 24 hours of onset to an SBP goal of less than 150 mmHg or less than 180 mmHg. The SBP target had to be achieved within 1 hour from randomization by means of intravenous antihypertensive agents. The aim of the study was to investigate the effect of intensive versus standard BP-lowering treatment on perihematoma CBF, which was measured by performing computed tomography perfusion imaging at 2 hours post-randomization in both groups. The results showed that intensive BP treatment was not associated with impairment of perihematoma CBF compared to the standard treatment group, contradicting the theory of cerebral ischaemia induced by BP lowering in ICH patients. Moreover, a post hoc analysis of ICH-ADAPT reported that early aggressive BP lowering was not associated with perihematoma oedema growth (27). These findings remain to be confirmed by a larger ongoing phase II trial (ClinicalTrials.gov ICH-ADAPT II, NCT02281838).

The promising observations regarding safety and feasibility from INTERACT1 and ATACH1 studies has led to the conduction of two large RCTs, aiming to investigate the impact of early aggressive BP lowering on clinical outcome in acute ICH.

INTERACT2 was an international, prospective, randomized, open-label, blinded endpoint trial (28). The study randomized 2839 ICH patients with SBP levels between 150–200 mmHg within 6 hours of onset to an intensive (SBP <140 mmHg, achieved within 1 hour and maintained for 7 days) or a guideline-recommended SBP target (SBP <180 mmHg). The choice of antihypertensive treatment was based on the local availability of antihypertensive agents. The composite primary outcome of the study was death or major disability, defined as a modified Rankin Scale (mRS) score of 3–6 at 90 days, whilst the secondary outcomes included ordinal analysis of the

primary endpoint, all-cause mortality, health-related quality of life, duration of hospitalization, living in residential care facility, haematoma expansion, neurological deterioration and serious adverse events. At 3 months, the rates of death and severe disability did not differ significantly between the two groups, although the primary outcome was reduced by 25% in the intensive compared to the guideline treatment group. The effects of intensive BP control on the primary outcome were consistent across all prespecified subgroups. However, ordinal analysis demonstrated a significantly favourable functional outcome for patients randomized to intensive BP-lowering treatment compared to their counterparts. Furthermore, intensive BP treatment was safe and associated with significantly better health-related quality of life than standard BP treatment. In contrast, the two groups did not differ significantly in terms of all-cause mortality and haematoma expansion.

The most recent RCT, ATACH2, was a multicentre, open-label, blinded endpoint trial, which randomly assigned 1000 patients with acute ICH (haematoma volume <60 mL) and increased SBP levels >180 mmHg to an aggressive SBP target (110–139 mmHg) or a standard SBP target (140–179 mmHg) within 4.5 hours of symptom onset by means of intravenous nicardipine (29). The trial was designed to evaluate the potential benefits obtained with tight compared to standard SBP targets on the primary (death or severe disability [mRS >3] at 3 months) and secondary outcome measures (all-cause mortality, health-related quality of life, haematoma growth, neurological deterioration and serious adverse events). The two groups did not differ significantly regarding the primary and secondary outcomes of the study. Aggressive treatment group demonstrated non-significantly lower rates of haematoma growth. Moreover, patients in the intensive group presented increased rates of any serious adverse events at 3 months and significantly higher rates of renal adverse events at 7 days after randomization compared to the standard group. Thus, the results of ATACH2 trial suggest that aggressive BP-lowering treatment in acute ICH is not effective and potentially harmful.

A recent meta-analysis of the aforementioned studies demonstrated that aggressive BP lowering in the setting of acute ICH is safe, reduces the risk of ICH expansion (though not statistically significant) but does not improve functional outcome and mortality at 3 months (30).

Thus, the optimal management of BP at the acute phase of ICH remains still unresolved. The safety of aggressive BP lowering demonstrated in INTERACT2 was not confirmed by the ATACH2 study. Moreover, both trials failed to meet their primary and secondary outcomes of reducing death, severe disability and haematoma expansion at 3 months, with the exception of the favourable functional outcome observed in the ordinal analysis of disability in INTERACT2 for aggressively treated ICH patients. The failure of both trials to demonstrate a clear clinical benefit from intensive BP lowering could be attributed to several methodological aspects such as recruitment of patients at low risk for haematoma expansion, heterogeneity in management of hypertension, different admission SBP values and time-window for inclusion in the study. Future trials should further investigate the optimal BP target in patients with acute ICH in terms of hard outcomes, as well as the effect of aggressive BP lowering on haematoma expansion especially in ICH patients with large haematomas and

increased intracranial pressure, who are at increased risk for cerebral hypoperfusion.

## GUIDELINES

### ISCHAEMIC STROKE

The American Heart Association/American Stroke Association (AHA/ASA) and the European Stroke Organization (ESO) have released guidelines regarding the management of high BP in the acute phase of IS (31,32). Both authorities recommend that in acute IS patients who are not candidates for thrombolysis, BP should not be lowered unless BP levels exceed 220/120 mmHg (threshold values recommended by consensus). If repeated BP measurements reveal SBP >220 mmHg and/or DBP >120 mmHg, pharmacological intervention is indicated, and BP should be reduced by no more than 15% in order to avoid profound BP falls that have been associated with neurological and functional worsening. Immediate onset of antihypertensive treatment is recommended in patients with acute stroke and target-organ damage such as acute myocardial infarction, left ventricular heart failure, acute renal failure, aortic dissection and hypertensive encephalopathy, independent of BP levels. Intravenous administration of antihypertensive drugs is superior to oral administration due to easier titration and better BP management under close BP monitoring (Table 58.3). Sublingual administration of nifedipine should be avoided because of the risk of abrupt BP drop and possible ischaemic steal. Regarding the optimal timing of restarting antihypertensive treatment in acute IS patients with BP levels below 220/120 mmHg and without comorbid conditions requiring acute antihypertensive therapy, the recently published AHA guidelines for management of high BP in adults recommend that initiating or reinitiating antihypertensive treatment within 48–72 hours after stroke onset is not effective to prevent death or dependency (33).

In acute IS patients eligible for thrombolysis, immediate parenteral antihypertensive treatment should be initiated if SBP >185 mmHg and/or DBP >110 mmHg, and BP levels should be maintained at desired levels (SBP <180 mmHg and DBP <105) during and for at least 24 hours after the thrombolysis. During this period, BP should be closely monitored, every 15 minutes for 2 hours from the initiation of the thrombolysis, then every 30 minutes for 6 hours and then every hour for the next 16 hours.

### INTRACEREBRAL HAEMORRHAGE

The novel findings of randomized controlled trials (INTERACT1, ATACH1, INTERACT2 and ICH-ADAPT) have influenced the AHA/ASA and the ESO and forced them to modify the previously published recommendations on BP management in acute haemorrhagic stroke. Currently, the AHA/ASA guidelines, published in 2015, for the management of spontaneous intracerebral haemorrhage recommend that for ICH patients with elevated SBP between 150–220 mmHg, early SBP lowering to 140 mmHg is safe and may improve functional outcome (34). In a similar way, the ESO guidelines, published in

**Table 58.3** Proposed antihypertensive agents for the management of arterial hypertension in acute stroke patients*Intravenously*

Labetalol 10–20 mg over 1–2 min, may repeat or double every 10 min (maximum 300 mg)  
 Nicardipine 5 mg/h infusion as initial dose, titrate to desired effect by increasing 2.5 mg/h every 5 min (maximum 15 mg/h)  
 Nitroprusside 0.5 µg/kg/min as initial dose with continuous BP monitoring  
 Urapidil 10–50 mg, followed by 4–8 mg/h  
 Nitroglycerin 5 mg, followed by 1–4 mg/h  
 Esmolol 500 µg/kg loading dose; maintenance use 50–200 µg/kg/min

*Subcutaneously*

Clonidine 0.15–0.30 mg

*Transdermally*

Glyceryl trinitrate 5 mg

*Sublingually*

Lisinopril 5 mg

*Orally*

Angiotensin converting inhibitors or angiotensin II receptor blockers with or without diuretic (secondary stroke prevention)

2014, state that in patients with acute ICH, early (within 6 hours of onset) aggressive BP lowering (SBP <140 mmHg within 1 hour of treatment initiation) is safe and may be superior to a less tight SBP target (>140 mmHg) (35). However, the results of ATACH2 study have dampened the enthusiasm of early aggressive BP lowering in these patients and forced the recently published AHA and the European Society of Hypertension guidelines on management of arterial hypertension to state that immediate BP lowering to less than 140 mmHg within 6 hours of the index event in patients with ICH and initial BP values between 150–220 mmHg is not of benefit to reduce death and severe disability, and can be potentially harmful (33,36).

Thus further randomized controlled studies are needed to define the optimal BP management in the acute phase of stroke. Until then, the BP goal in acute stroke will remain a matter of considerable debate.

## REFERENCES

- Lewington S, Clarke R, Qizilbash N et al. Prospective studies collaboration: Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360: 1903–1913.
- Qureshi AI, Ezzeddine MA, Nasar A et al. Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. *Am J Emerg Med* 2007; 25: 32–38.
- Britton M, Carlsson A, de Faire U. Blood pressure course in patients with acute stroke and matched controls. *Stroke* 1986; 17: 861–864.
- Ahmed N, Nasman P, Wahlgren NG. Effect of intravenous nimodipine on blood pressure and outcome after acute stroke. *Stroke* 2000; 31: 1250–1255.
- Leonardi-Bee J, Bath PM, Phillips SJ et al. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke* 2002; 33: 1315–1320.
- Vemmos KN, Tsiygoulis G, Spengos K et al. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. *J Intern Med* 2004; 255: 257–265.
- Vemmos KN, Tsiygoulis G, Spengos K et al. Association between 24-h blood pressure monitoring variables and brain oedema in patients with hyperacute stroke. *J Hypertens* 2003; 21: 2167–2173.
- Schrader J, Lóders S, Kulschewski A et al. The ACCESS study: Evaluation of acute candesartan cilexetil therapy in stroke survivors. *Stroke* 2003; 34: 1699–1703.
- Sandset EC, Bath PM, Boysen G et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): A randomised, placebo-controlled, double-blind trial. *Lancet* 2011; 377: 741–750.
- Jusufovic M, Sandset EC, Bath PM et al. Effects of blood pressure lowering in patients with acute ischemic stroke and carotid artery stenosis. *Int J Stroke* 2015; 10: 354–359.
- Potter JF, Robinson TG, Ford GA et al. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): A randomised, placebo-controlled, double-blind pilot trial. *Lancet Neurol* 2009; 8: 48–56.
- Robinson TG, Potter JF, Ford GA et al. Effects of antihypertensive treatment after acute stroke in the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS): A prospective, randomised, open, blinded-endpoint trial. *Lancet Neurol* 2010; 9: 767–775.
- He J, Zhang Y, Xu T et al. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: The CATIS randomized clinical trial. *JAMA* 2014; 311: 479–489.
- Bath PM, Woodhouse L, Scutt P et al. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): A partial-factorial randomised controlled trial. *Lancet* 2015; 385: 617–628.
- Ahmed N, Wahlgren N, Brainin M et al. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis. Retrospective analysis from Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). *Stroke* 2009; 40: 2442–2449.
- Willmot M, Leonardi-Bee J, Bath PMW. High blood pressure in acute stroke and subsequent outcome: A systematic review. *Hypertension* 2004; 43: 18–24.
- Ohwaki K, Yano E, Nagashima H et al. Blood pressure management in acute intracerebral hemorrhage: Relationship between elevated blood pressure and hematoma enlargement. *Stroke* 2004; 35: 1364–1367.
- Brott T, Broderick J, Kothari R et al. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke* 1997; 28: 1–5.
- Qureshi AI, Mohammad YM, Yahia AM et al. A prospective multicenter study to evaluate the feasibility and safety of aggressive antihypertensive treatment in patients with acute intracerebral hemorrhage. *J Intensive Care Med* 2005; 20: 34–42.
- Davis SM, Broderick J, Hennerici M et al. Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology* 2006; 66: 1175–1181.
- Broderick JP, Brott TG, Duldner JE et al. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. *Stroke* 1993; 24: 987–993.
- Delcourt C, Huang Y, Arima H et al. Hematoma growth and outcomes in intracerebral hemorrhage: The INTERACT1 study. *Neurology* 2012; 79: 314–319.



23. Anderson CS, Huang Y, Wang JG et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): A randomised pilot trial. *Lancet Neurol* 2008; 7: 391–399.
24. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) investigators. Antihypertensive treatment of acute cerebral hemorrhage. *Crit Care Med* 2010; 38: 637–648.
25. Qureshi A, Palesch Y, Martin R et al. Effect of systolic blood pressure reduction on hematoma expansion, perihematomal edema, and 3-month outcome among patients with intracerebral hemorrhage. *Arch Neurol* 2010; 67: 570–576.
26. Butcher KS, Jeerakathil T, Hill M et al. The intracerebral hemorrhage acutely decreasing arterial pressure trial (ICH-ADAPT). *Stroke* 2013; 44: 620–626.
27. McCourt R, Gould B, Gioia L et al. Cerebral perfusion and blood pressure do not affect perihematoma edema growth in acute intracerebral hemorrhage. *Stroke* 2014; 45: 1292–1298.
28. Anderson CS, Heeley E, Huang Y et al. Rapid blood pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med* 2013; 368: 2355–2365.
29. Qureshi AI, Palesch YY, Barsan WG et al. Intensive blood pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med* 2016; 375: 1033–1043.
30. Boulouis G, Morotti A, Goldstein J et al. Intensive blood pressure lowering in patients with acute intracerebral hemorrhage: Clinical outcomes and hemorrhage expansion, Systematic review and meta-analysis of randomized trials. *JNNP* 2017; 88: 339–345.
31. Jauch EC, Saver JL, Adams HP Jr et al. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; 44: 870–947.
32. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. *Cerebrovasc Dis* 2008; 25: 457–507.
33. Whelton PK, Carey RM, Aronow WS et al. Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardio* 2017. DOI: 10.1016/j.jacc.2017.07.74.
34. Hemphill JC 3rd, Greenberg SM, Anderson CS et al. Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2015; 46: 2032–2060.
35. Steiner T, Al-Shahi Salman R, Beer R et al. European stroke organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke* 2014; 9: 840–855.
36. Williams B, Mancia G, Spiering W et al. ESC/ESH Guidelines for the management of arterial hypertension. *J Hypertens* 2018; 36: 1953–2041.





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# BLOOD PRESSURE MANAGEMENT IN THE CHRONIC POST-STROKE PHASE

# 59

*Hisatomi Arima and John Chalmers*

## INTRODUCTION

Annually, 17 million people worldwide suffer a stroke (1). Of these, 6 million die and another 6 million are left permanently disabled, placing a burden on family and community (1). Among those who survive a stroke or a transient ischaemic attack (TIA), the risk of further stroke is very high (2,3). Stroke survivors also face increased risks of other manifestations of atherosclerosis and degenerative vascular disease, such as coronary heart disease (3,4), peripheral vascular disease and cognitive decline (5,6). While the incidence of stroke is declining in many developed countries, the absolute number of strokes continues to increase globally due to progressive ageing of populations (1).

Stroke incidence is associated with a number of modifiable and nonmodifiable risk factors, but ten major modifiable risk factors (high blood pressure, current smoking, high waist-to-hip ratio, unhealthy diet, physical inactivity, diabetes, excessive alcohol intake, cardiac disease and dyslipidaemia) have been shown to account for 90% of the population attributable risk of stroke in the INTERSTROKE study (7). Among those, high blood pressure is the dominant modifiable risk factor, accounting for 48% of the population attributable risk of stroke. Thus, blood pressure-lowering treatment is likely to be the single most important stroke prevention strategy.

There is now strong evidence from randomised controlled trials that blood pressure-lowering treatment is one of the most effective interventions for both primary and secondary prevention of stroke (8–10). Furthermore, blood pressure-lowering treatment provides the only proven strategy for the secondary prevention of intracerebral haemorrhage. This article reviews the results obtained from the randomised controlled trials, focussing on blood pressure-lowering treatment for secondary prevention of stroke.

## EVIDENCE FROM RANDOMISED TRIALS

Randomised trials have clearly demonstrated that blood pressure-lowering treatment reduces the risk of initial stroke (8,9). In contrast, before the results of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS)

were published in 2001, there was little convincing evidence that blood pressure-lowering treatment would reduce the incidence of recurrent stroke in patients with cerebrovascular disease. More evidence was provided in the mid-1990s by a preliminary report from a randomised trial of diuretics among 5665 individuals with a history of cerebrovascular disease (the Post-Stroke Antihypertensive Study [PATS]) (11) and by a systematic review of subsets of stroke survivors in randomised trials of blood pressure-lowering treatment performed by the Individual Data Analysis of Antihypertensive Intervention Trials (INDANA) Project Collaborators (12). PATS suggested that blood pressure-lowering treatment with the diuretic indapamide reduced the risk of recurrent stroke by 27% (95% confidence interval [CI] 11–40%), though the disadvantage of PATS is the fact that the complete data have not been published internationally (11). The systematic review by INDANA Project Collaborators suggested that blood pressure-lowering treatment would reduce the risk of recurrent stroke by 28% (95% CI 15–39%) in mainly hypertensive subjects with prior cerebrovascular disease (12). However, these data were insufficient to determine the benefits of blood pressure lowering in normotensive subjects with cerebrovascular disease.

Definite evidence of beneficial effects of blood pressure-lowering treatment for secondary prevention of stroke was provided in 2001 by the PROGRESS trial (13,14). The PROGRESS trial was a randomised, placebo-controlled trial that clearly established the benefits of perindopril-based blood pressure lowering in a heterogeneous group of patients with cerebrovascular disease. A total of 6105 patients with prior stroke or TIA were randomly assigned to either active treatment (an angiotensin-converting enzyme [ACE] inhibitor, perindopril [4 mg daily], for all participants plus a diuretic, indapamide [2–2.5 mg daily], for those with neither an indication for, nor a contraindication to, a diuretic) or matching placebo(s). Over a mean follow-up of 4 years, the overall relative risk of recurrent stroke was reduced by 28% (95% CI 17–38%) in the active treatment group compared to the placebo group. PROGRESS trial also demonstrated that the benefits of treatment were comparable for patients that were and were not hypertensive at baseline, using a cutoff of 160/90 mmHg in accord with the evidence available in

1994 when the trial was initiated. This resolved the issue in normotensive subjects with cerebrovascular disease that previous trials had left unanswered.

In the PROGRESS trial, combination therapy with perindopril plus indapamide produced consistently larger reductions in the risk of stroke (43%, 95% CI 30–54%) compared to single-drug therapy with perindopril (5%, 95% CI –19 to 23%, non-significant reduction), and it is likely that the large differences in treatment effect represent the benefits of greater blood pressure reduction with combination therapy with perindopril plus indapamide compared to single-drug therapy with perindopril (12/5 mmHg vs. 5/3 mmHg) (13).

Several randomised controlled trials completed after PROGRESS have reported the effects of blood pressure lowering on recurrent stroke. The Felodipine Event Reduction (FEVER) study has also demonstrated a trend towards reduction in recurrent stroke in a subset of 2368 patients with a history of stroke or TIA (relative risk reduction 18% [95% CI –12 to 40%]), associated with a modest reduction in blood pressure (4.0/1.8 mmHg), obtained with a calcium channel blocker (CCB) felodipine (15). While many trials completed after PROGRESS have broadly confirmed our findings, the results of the Prevention Regimen For Effectively Avoiding Second Strokes (PROFESS) study (16), which was published in 2008, were less positive. The PROFESS trial investigated the effects of an angiotensin receptor blocker (ARB) telmisartan in addition to standard care for secondary prevention of stroke among 20,322 patients with recent ischaemic stroke. Active treatment lowered blood pressure by 4/2 mmHg and reduced the risk of recurrent stroke by 5% (95% CI –4 to 14%). Although telmisartan did not confirm significant benefit, factors that might have contributed to the negative outcome include the small difference in blood pressure between randomised groups, a large number of patients with a history of large artery infarction (30%), and the frequent use of ACE inhibitors (37%), that had already achieved a moderate degree of blood pressure control at baseline (144/84 mmHg). The Secondary Prevention of Small Subcortical Strokes (SPS3) trial was the first trial to investigate the effects of intensive blood pressure lowering with target systolic blood pressure levels of <130 mmHg among 3020 patients with symptomatic lacunar infarction. After 1 year, mean systolic blood pressure was 11 mmHg lower in the intensive blood pressure-lowering group than in the control group. Non-significant rate reductions were observed for the primary outcome of total recurrent stroke (hazard ratio [HR] 0.81, 95% CI 0.64–1.03), while the rate of intracerebral haemorrhage was reduced significantly (0.37, 0.15–0.95). Non-significant associations for total stroke in SPS3 might be attributable to limited statistical power due to smaller number of events than expected (277 vs. more than 500 events).

Our updated meta-analysis of 23 randomised controlled trials (17 active vs. control, 3 more vs. less intensive, and 3 ARB vs. CCB) including PROGRESS, FEVER, PROFESS and SPS3 with a total of 49,195 patients demonstrates that blood pressure-lowering treatment clearly reduced the risk of recurrent stroke (relative risk reduction [RRR] 22%, 95% CI 12–30%) (Figure 59.1). Thus, the totality of the evidence, including the findings from PROFESS and SPS3, confirms that blood pressure-lowering treatment reduces the risk of stroke recurrence among patients with cerebrovascular disease.

## THRESHOLD FOR BLOOD PRESSURE LOWERING AND OPTIMAL TARGET BLOOD PRESSURE IN SECONDARY PREVENTION OF STROKE

With regard to threshold for blood pressure lowering, a subsidiary analysis of the PROGRESS trial investigated the effects of randomised treatment on recurrent stroke by baseline blood pressure levels (Figure 59.2) (17). Blood pressure lowering with combination therapy of perindopril plus indapamide produced similar risk reductions in each of subgroups defined by baseline systolic blood pressure of less than 120, 120–139, 140–159 and 160 mmHg or greater ( $p$  homogeneity = 0.5) and those defined by baseline diastolic blood pressure of less than 80, 80–89, 90–99 and 100 mmHg or greater ( $p$  homogeneity = 0.2). The effects of single-drug therapy with perindopril alone were also comparable across these subgroups ( $p$  homogeneity = 0.2 and 0.8 for systolic and diastolic blood pressure, respectively), but consistently greater benefits were observed with combination compared to single-drug therapy. It is clear that blood pressure-lowering treatment should be considered routinely for patients with a history of stroke or TIA, irrespective of their blood pressure.

With regard to optimal target blood pressure, large-scale observational studies have demonstrated clear associations between blood pressure and initial stroke (18,19). A systematic review of observational studies performed by the Prospective Studies Collaboration demonstrated that lower blood pressure levels are continuously associated with lower risks of fatal stroke down to very low blood pressure levels (as low as 115/75 mmHg) (18). A continuous relationship of blood pressure with the outcome 'fatal and non-fatal stroke' was also observed down to levels as low as 115/75 mmHg in a systematic review performed by the Asia Pacific Cohort Studies Collaboration (19). More limited evidence from studies in patients with a history of cerebrovascular disease has also suggested that lower blood pressure levels are associated with lower risks of stroke recurrence. A large-scale observational study demonstrated that the relationship between blood pressure levels and recurrent stroke was strong and continuous down to levels of 130/80 mmHg (20). In addition, an observational analysis of PROGRESS showed that the lowest risk of recurrent stroke was observed amongst individuals who achieved a follow-up blood pressure of approximately 115/75 mmHg (Figure 59.3) (17). Similar relationships were observed for both ischaemic stroke and intracerebral haemorrhage (Figure 59.3) (17). In contrast, an observational analysis from PROFESS demonstrated slight increase in the risks of recurrent stroke among patients who achieved systolic blood pressure levels of less than 120 mmHg (21), although the modest increase in very low systolic blood pressure levels disappeared after exclusion of patients within 6 months from stroke onset. These observational data suggest that, in chronic, stable phase after stroke, lower blood pressure levels are continuously associated with lower risks of recurrence, down to very low blood pressure levels (115 mmHg systolic).

There are also a few randomised controlled trials which investigated the benefits and harms of intensive blood pressure lowering towards lower systolic blood pressure levels in secondary prevention of stroke. As described in the previous section of this chapter, SPS3 trial demonstrated non-significant

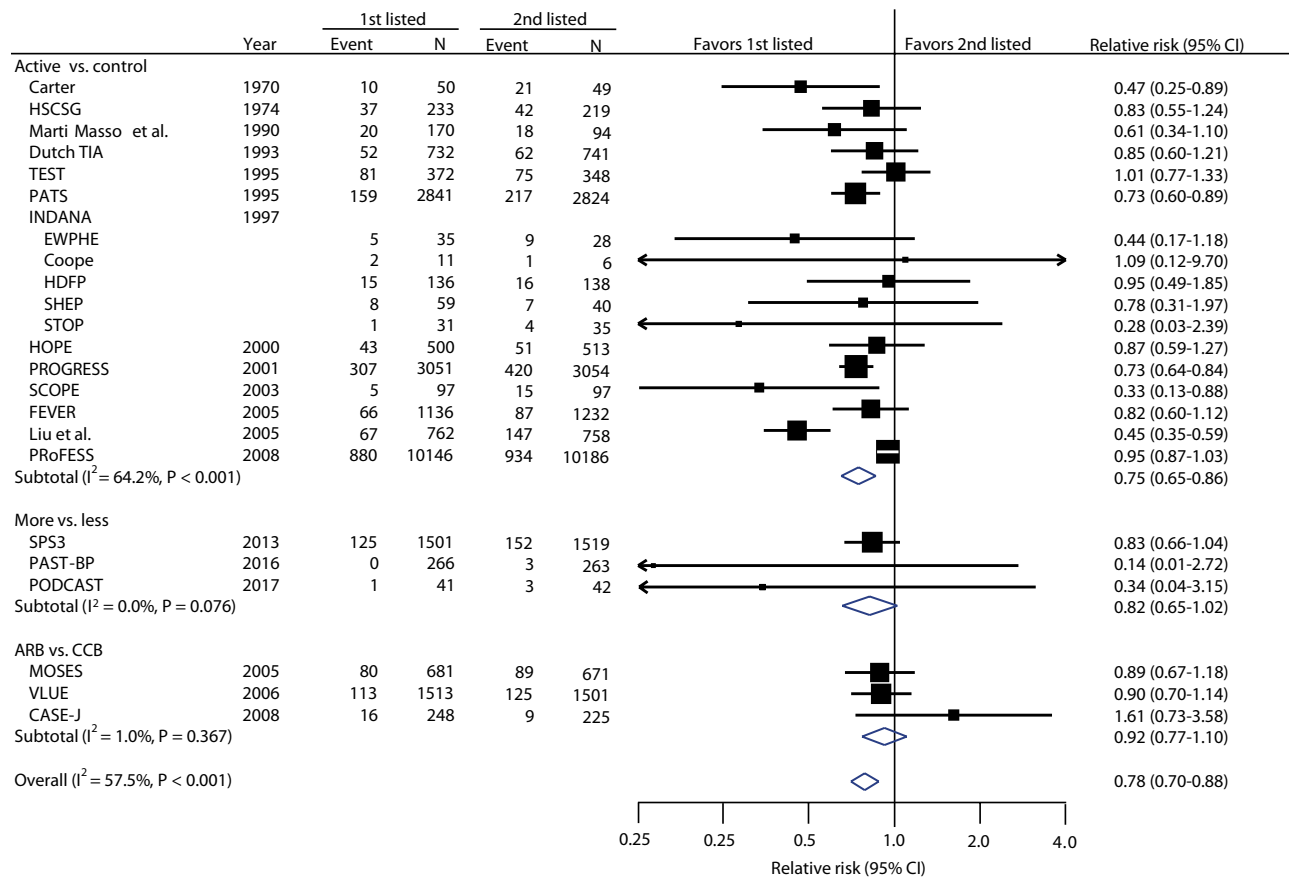


**Figure 59.1** Meta-analysis of 16 randomised controlled trials of blood pressure lowering for secondary prevention of stroke. Solid boxes represent estimates of trials; areas of the boxes are proportional to the inverse variance of the estimates; vertical lines represent 95% CI; diamonds represent estimates and 95% CI for overall effects. Overall estimates of effect and 95% CI were calculated using random-effects models and inverse variance weighting.

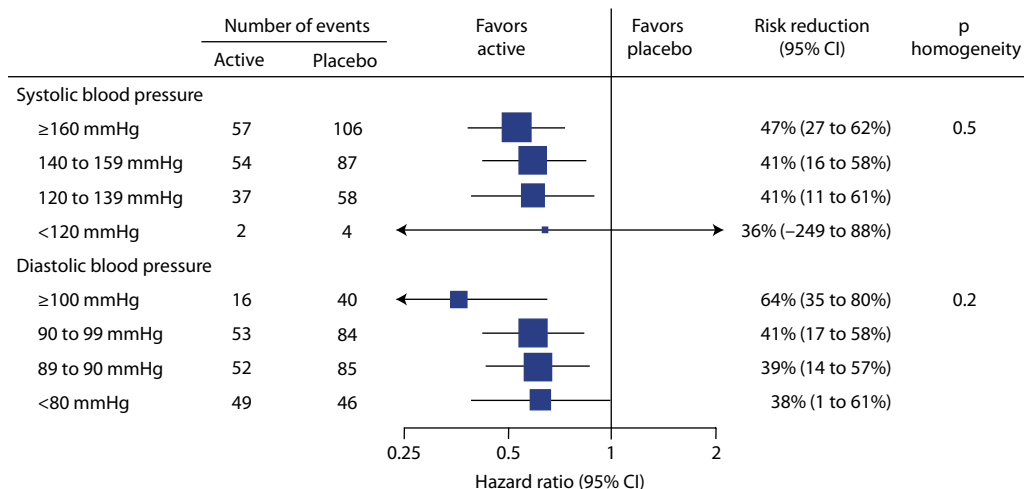
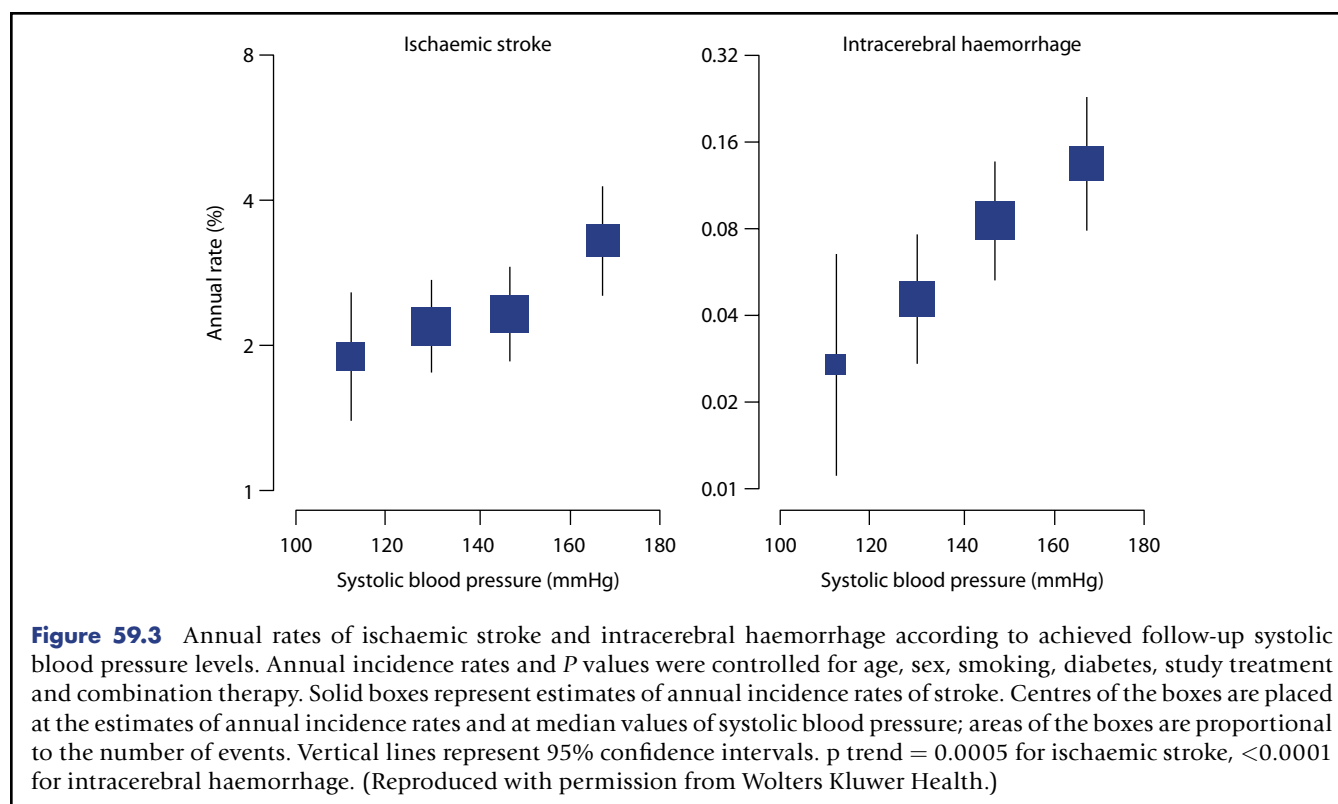


**Figure 59.2** Effects of blood pressure lowering with combination therapy of perindopril plus indapamide on stroke by baseline blood pressure. Solid boxes represent estimates of hazard ratio for stroke; areas of the boxes are proportional to the inverse variance of the estimates; vertical lines represent 95% CI. (Adapted from previously published figures with permission from Wolters Kluwer Health.)



reduction in recurrent stroke (HR 0.81; 95% CI 0.64–1.03) among patients who received intensive blood pressure lowering with target systolic blood pressure levels of <130 mmHg among 3020 patients with symptomatic lacunar infarction. The Prevention After Stroke—Blood Pressure (PAST-BP) (22) and the pilot Prevention of Decline in Cognition after Stroke Trial (PODCAST) (23) also investigated the effects of intensive blood pressure lowering (target systolic blood pressure level <130 mmHg for PAST-BP and <125 mmHg for PODCAST) in the setting of secondary prevention of stroke. However, there are limited number of recurrent stroke events because of relatively small sample size and short follow-up duration (PAST-BP: 529 patients for 1 year, PODCAST: 83 patients for 2 years). When SPS3, PAST-BP and PODCAST are pooled, there is marginally significant 18% reduction (95% CI –2 to 35) in the risk of recurrent stroke associated with intensive blood pressure lowering with target systolic blood pressure <130 mmHg (*P* = 0.076) (Figure 59.1). Definitive evidence of intensive blood pressure lowering for prevention of stroke will be provided by ongoing trials such as Recurrent Stroke Prevention Clinical Outcome Study (RESPECTS), the Stroke in Hypertension Optimal Treatment Trial (ESH-CHL-SHOT) and Triple Therapy Prevention of Recurrent Intracerebral Disease Events Trial (TRIDENT). Meanwhile, in keeping with the current international guidelines (24,25), we would recommend that blood pressure should be lower to less than 130/80 mmHg in patients with stroke or TIA.

### PATIENTS WITH LARGE ARTERY STENOSIS

A contentious area of blood pressure-lowering treatment in chronic post-stroke phase is the risks and benefits in

patients with severe large artery occlusive diseases. Among patients with severe occlusive disease of extracranial and intracranial large arteries, cerebral perfusion may depend on blood pressure, and intensive blood pressure-lowering treatment may lead to ischaemic stroke via hemodynamic mechanisms. As patients with stenosis in large arteries are also likely to have atherosclerotic lesions in various large arteries including coronary, renal and peripheral arteries, intensive blood pressure lowering may result in hypoperfusion and subsequent damage in various organs. An observational study of the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial investigated the association between blood pressure and ischaemic stroke among 567 patients with cerebrovascular disease due to angiographically verified 50–99% stenosis of a large artery (26). Among patients with moderate large artery stenosis (50–69%), systolic blood pressure was associated with increased risk of ischaemic stroke. Among patients with severe large artery stenosis (70–99%), in contrast, systolic blood pressure was not significantly associated with the risk of ischaemic stroke. Furthermore, a meta-analysis of European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial (NASCET) investigated the association of systolic blood pressure and stroke among patients with cerebrovascular disease and severe, symptomatic stenosis (70% or more) in both carotid arteries and found that lower systolic blood pressure was associated with increased risks of stroke (27). These results suggest that intensive blood pressure lowering may be harmful among patients with severe, symptomatic stenosis in both sides of the cerebral circulation. For patients at high risk of cardiovascular disease, it would be useful to provide comprehensive screening of clinical and subclinical atherosclerotic lesions in coronary, renal, peripheral and other arteries as well as carotid and



intracranial arteries. If there is severe occlusive or stenotic large artery disease, treatment of the arterial lesions may be taken into consideration before starting intensive blood pressure-lowering treatment.

## DIFFERENT CLASSES OF BLOOD PRESSURE-LOWERING DRUGS AND COMBINATION THERAPIES

There are insufficient data to determine whether one class of drugs is superior to another in the secondary prevention of stroke. The Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated that an ACE inhibitor ramipril reduced the risk of recurrent stroke by approximately 25% among a subgroup of 1013 patients with history of cerebrovascular disease (28). PROGRESS has clearly demonstrated the beneficial effects of combination therapy with the ACE inhibitor perindopril plus the diuretic indapamide in secondary prevention of stroke (13). Clinicians wishing to practice in accord with the tenets of Evidence-Based Medicine (EBM) should use combination therapy with ACE inhibitors plus thiazide-like diuretics, such as indapamide, which was shown to be effective in the PROGRESS (13), unless there are contraindications.

In regard to ARB, the PRoFESS trial failed to demonstrate the beneficial effects of the ARB telmisartan in secondary prevention of stroke (16) but non-significant reduction in recurrent stroke is likely to be largely attributable to small difference in blood pressure between randomised groups. In contrast, the Study on Cognition and Prognosis in the Elderly (SCOPE) trial also demonstrated beneficial effects of the ARB candesartan on recurrent stroke (29). Meta-analysis of the Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES) (30), Valsartan Antihypertensive Long-term Use Evaluation (VALUE) (31) and Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) (32), which compared the effects of ARB with those of CCB among patients with prior stroke, also demonstrated non-significant 8% reduction of recurrent stroke in the ARB group (95% CI –10 to 23) (Figure 59.1).

CCBs also require consideration for secondary prevention of stroke. The systematic review of BPLTTC showed trends towards greater efficacy of CCBs compared to other drug classes for primary prevention of stroke, although these trends may have reflected greater blood pressure reduction with CCBs (33). This was reinforced by the meta-analysis of 147 randomised trials reported by Law et al. (34). The FEVER trial has also demonstrated modest reduction in recurrent stroke associated with the CCB felodipine (15). Therefore, it would seem reasonable to use a CCB in the chronic post-stroke phase.

Because most hypertensive patients require combination therapies and the current large gap between target and achieved blood pressure levels has been shown to be largely attributable to reliance on the use of single drugs (35), building effective combinations is essential. The recent American 2017 guidelines recommended initiation of combination therapy with two first-line agents of different classes for patients with elevated blood pressure levels of 140/90 mmHg or higher and more than 20/10 mmHg above their blood pressure target (24). With regard to chronic post-stroke phase, the first-line combination

would be ACE inhibitors plus thiazide-like diuretics, which was shown to be effective in the PROGRESS trial (13). Combination of ACE inhibitor and CCB as confirmed by Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure-Lowering Arm (ASCOT-BPLA) (36) and Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial (37), ARB and CCB, ARB and diuretics, and CCB and diuretics are also recommended by guidelines for management of hypertension (25).

## CONCLUSIONS

A number of randomised controlled trials and their meta-analyses have clearly demonstrated beneficial effects of perindopril-based blood pressure-lowering treatment for the prevention of recurrent stroke and other cardiovascular events in a heterogeneous group of patients with prior stroke or a TIA. As blood pressure-lowering treatment produced similar risk reductions across a wide range of baseline blood pressure levels, all patients who have suffered a completed stroke or TIA should receive blood pressure-lowering therapy whether hypertensive or not. On the basis of the totality of evidence presently available, and in keeping with the current international guidelines (24,25), we would recommend that blood pressure should be lowered to less than 130/80 mmHg in patients with previous stroke or TIA.

## REFERENCES

1. Feigin VL, Forouzanfar MH, Krishnamurthi R et al. Global and regional burden of stroke during 1990–2010: Findings from the Global Burden of Disease Study 2010. *Lancet* 2014; 383: 245–254.
2. Brown DL, Lisabeth LD, Roychoudhury C et al. Recurrent stroke risk is higher than cardiac event risk after initial stroke/transient ischemic attack. *Stroke* 2005; 36: 1285–1287.
3. Arima H, Tzourio C, Butcher K et al. Prior events predict cerebrovascular and coronary outcomes in the PROGRESS trial. *Stroke* 2006; 37: 1497–1502.
4. Adams RJ, Chimowitz MI, Alpert JS et al. Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke: A scientific statement for healthcare professionals from the Stroke Council and the Council on Clinical Cardiology of the American Heart Association/American Stroke Association. *Stroke* 2003; 34: 2310–2322.
5. Kokmen E, Whisnant JP, O'Fallon WM et al. Dementia after ischemic stroke: A population-based study in Rochester, Minnesota (1960–1984). *Neurology* 1996; 46: 154–159.
6. Pohjasvaara T, Erkinjuntti T, Vataja R et al. Dementia three months after stroke. Baseline frequency and effect of different definitions of dementia in the Helsinki Stroke Aging Memory Study (SAM) cohort. *Stroke* 1997; 28: 785–792.
7. O'Donnell MJ, Chin SL, Rangarajan S et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): A case-control study. *Lancet* 2016; 388: 761–775.
8. Ettehad D, Emdin CA, Kiran A, Anderson SG et al. Blood pressure lowering for prevention of cardiovascular disease and death: A systematic review and meta-analysis. *Lancet* 2016; 387: 957–967.
9. Xie X, Atkins E, Lv J et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: Updated systematic review and meta-analysis. *Lancet* 2016; 387: 435–443.
10. Katsanos AH, Filippatou A, Manios E et al. Blood pressure reduction and secondary stroke prevention: A systematic review and metaregression analysis of randomized clinical trials. *Hypertension* 2017; 69: 171–179.
11. PATS Collaborating Group. Post-stroke antihypertensive treatment study: A preliminary result. *Chin Med J* 1995; 108: 710–717.
12. The INDANA (INDividual Data ANALysis of Antihypertensive intervention trials) Project Collaborators. Effect of

- antihypertensive treatment in patients having already suffered from stroke: Gathering the evidence. *Stroke* 1997; 28: 2557–2562.
13. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood pressure lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; 358: 1033–1041.
  14. Arima H, Chalmers J. PROGRESS: Prevention of recurrent stroke. *J Clin Hypertens (Greenwich)* 2011; 13: 693–702.
  15. Liu L, Wang Z, Gong L et al. Blood pressure reduction for the secondary prevention of stroke: A Chinese trial and a systematic review of the literature. *Hypertens Res* 2009; 32: 1032–1040.
  16. Yusuf S, Diener HC, Sacco RL et al. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med* 2008; 359: 1225–1237.
  17. Arima H, Chalmers J, Woodward M et al. Lower target blood pressures are safe and effective for the prevention of recurrent stroke: The PROGRESS trial. *J Hypertens* 2006; 24: 1201–1208.
  18. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360: 1903–1913.
  19. Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular diseases in the Asia-Pacific region. *J Hypertens* 2003; 21: 707–716.
  20. Rodgers A, MacMahon S, Gamble G et al. Blood pressure and risk of stroke in patients with cerebrovascular disease. *BMJ* 1996; 313: 147.
  21. Ovbiagele B, Diener HC, Yusuf S et al. Level of systolic blood pressure within the normal range and risk of recurrent stroke. *JAMA* 2011; 306: 2137–2144.
  22. Mant J, McManus RJ, Roalfe A et al. Different systolic blood pressure targets for people with history of stroke or transient ischaemic attack: PAST-BP (Prevention After Stroke—Blood Pressure) randomised controlled trial. *BMJ* 2016; 352: i708.
  23. Bath PM, Scutt P, Blackburn DJ et al. Intensive versus guideline blood pressure and lipid lowering in patients with previous stroke: Main results from the pilot 'Prevention of Decline in Cognition after Stroke Trial' (PODCAST) randomised controlled trial. *PLOS ONE* 2017; 12: e0164608.
  24. Whelton PK, Carey RM, Aronow WS et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2017; 71(6): 1269–1324.
  25. Williams B, Mancia G, Spiering W et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *J Hypertens* 2018; 36: 1953–2041.
  26. Turan TN, Cotsonis G, Lynn MJ et al. Relationship between blood pressure and stroke recurrence in patients with intracranial arterial stenosis. *Circulation* 2007; 115: 2969–2975.
  27. Rothwell PM, Howard SC, Spence JD For the Carotid Endarterectomy Trialists' Collaboration. Relationship between blood pressure and stroke risk in patients with symptomatic carotid occlusive disease. *Stroke* 2003; 34: 2583–2592.
  28. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; 342: 145–153.
  29. Trenkwalder P, Elmfeldt D, Hofman A et al. The Study on COgnition and Prognosis in the Elderly (SCOPE)—major CV events and stroke in subgroups of patients. *Blood Press* 2005; 14: 31–37.
  30. Schrader J, Luders S, Kulschewski A et al. Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: Principal results of a prospective randomised controlled study (MOSES). *Stroke* 2005; 36: 1218–1226.
  31. Zanchetti A, Julius S, Kjeldsen S et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: An analysis of findings from the VALUE trial. *J Hypertens* 2006; 24: 2163–2168.
  32. Ogiwara T, Nakao K, Fukui T et al. The optimal target blood pressure for antihypertensive treatment in Japanese elderly patients with high-risk hypertension: a subanalysis of the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial. *Hypertens Res* 2008; 31: 1595–1601.
  33. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: Results of prospectively-designed overviews of randomised trials. *Lancet* 2003; 362: 1527–1535.
  34. Law MR, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009; 338: b1665.
  35. Chow CK, Teo KK, Rangarajan S et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA* 2013; 310: 959–b1968.
  36. Dahlöf B, Sever PS, Poulter NR et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): A multicentre randomised controlled trial. *Lancet* 2005; 366: 895–906.
  37. Jamerson K, Weber MA, Bakris GL et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008; 359: 2417–2428.

# THE POST-TRANSPLANT PATIENT WITH HYPERTENSION

# 60

*Martin Hausberg and Karl Heinz Rahn*

## INTRODUCTION

Hypertension is a common problem after solid organ transplantation and affects primarily the recipients of kidney, heart and liver transplants. Significant causes are the use of calcineurin inhibitors as immunosuppressive drugs and progressive deterioration of kidney function. The situation in kidney transplant recipients is more complex and is discussed in detail below.

The prognostic relevance of hypertension in heart and liver transplant recipients is not yet clearly established. Myers and co-workers could not establish systemic arterial blood pressure as predictor of survival after heart transplantation (1). Also, in liver transplant recipients, Guckelberger and co-workers did not observe blood pressure as independent predictor of cardiovascular outcome (2). However, from the available evidence the management of hypertension in solid organ transplant recipients does not differ significantly with regard to the transplanted organ. Effective blood pressure control is mandatory not only in kidney transplant recipients but also in other solid organ transplant recipients. Ojo et al. reported a cumulative 5-year incidence of end-stage renal disease in nonrenal solid organ transplant recipients between 7–21% depending on the organ transplanted (3). A significant risk factor for renal failure was hypertension, and the occurrence of renal failure was associated with excess mortality (relative risk 4.55).

Since kidney transplant patients represent the majority of solid organ transplant recipients, causes of hypertension in nonrenal solid organ transplant recipients apply also to kidney transplant patients and the relevance of hypertension is best established after kidney transplantation, this review will now focus on hypertension after kidney transplantation.

## PREVALENCE OF ARTERIAL HYPERTENSION AFTER KIDNEY TRANSPLANTATION

Three decades ago, with modern immunosuppressants not available, only 30–40% of kidney transplant recipients developed hypertension. However, 1-year graft survival was

in general not much above 50% (4). The introduction of calcineurin inhibitors, first cyclosporine two decades ago, followed later by tacrolimus, greatly improved short-term graft survival in kidney transplant patients. One-year graft survival reached 80–90% after the introduction of cyclosporine (4). Unfortunately, the use of calcineurin inhibitors is associated with a large prevalence of hypertension in kidney transplant patients. More than 80% of patients develop hypertension during the first year after transplantation according to ISH/WHO criteria, that is, blood pressure values >140/90 mmHg (5). Schwenger and co-workers reported a single-centre survey, showing only 42.9% of renal allograft recipients with blood pressures <140/90 mmHg, 22.4% of patients with blood pressures <130/85 mmHg and mere 4.1% of patients with blood pressures <125/75 mmHg – despite antihypertensive treatment (6).

Moreover, ambulatory blood pressure profiles are disturbed in most patients after kidney transplantation. Interestingly, a correlation between serum creatinine and nighttime blood pressure change was reported (6). Patients with high serum creatinine concentrations (i.e. impaired graft function) showed a paradoxical nighttime increase in blood pressure.

## CAUSES OF HYPERTENSION IN KIDNEY TRANSPLANT PATIENTS

First, immunosuppressive treatment is to be noted. The calcineurin inhibitors cyclosporine and tacrolimus cause hypertension in kidney transplant patients, in recipients of heart (7) and liver transplants (8), but also unrelated to transplantation in patients with or without renal disease requiring immunosuppressive treatment (9) (Table 60.1). The mechanisms of calcineurin-inhibitor-induced hypertension have been best studied for cyclosporine. This drug causes acute decreases in renal plasma flow and glomerular filtration rate, mediated by vasoconstriction predominantly affecting the afferent glomerular arteriole (10). This contributes to enhanced tubular sodium absorption and resulting hypervolemia (11). The vasoconstrictor effects of cyclosporine are attributable to both enhanced pressor and decreased vasodilator mechanisms. Cyclosporine

**Table 60.1** Causes of hypertension after kidney transplantation

- Immunosuppressive drugs (e.g. calcineurin inhibitors and steroids)
- Alterations of large artery structure and function
- Progressive decline in graft function, due to
  - Chronic allograft nephropathy, including chronic rejection
  - Recurrence of primary renal disease in the graft
  - De novo glomerulonephritis in the graft
- Diseased native kidneys via
  - Secretion of humoral factors such as renin
  - Sympathetic activation by excitation of renal afferent nerves
- Stenosis of the graft artery
- Rare causes (e.g. post-transplant erythrocytosis, genetic factors linked to the graft)

activates the renin–angiotensin system (12), induces the expression of endothelin 1, and increases the production of thromboxane (13), all resulting in vasoconstriction. Moreover, cyclosporine may cause activation of the sympathetic nervous system. This could be well demonstrated in animal models (14), however, the results of human studies are equivocal (7,15). We could show only small acute increases in sympathetic nerve activity with cyclosporine in kidney transplant patients; tacrolimus had no effect. In contrast, we could not demonstrate any chronic sympathoexcitatory effect of cyclosporine. Cyclosporine withdrawal in renal transplant patients with chronic allograft nephropathy was associated with a decrease in blood pressure but sympathetic nerve activity remained elevated (16). Sympathetic activation by cyclosporine has been linked to excitation of renal afferent nerves which depend on synapsin in afferent nerve endings (17). It is conceivable that the synapsin-mediated activation of renal sensory nerves is disturbed in kidney transplant patients who have severely diseased native kidneys and denervated grafts. Therefore cyclosporine may not induce any additional activation of renal afferent nerves in patients with renal disease.

Beyond these pressor effects, cyclosporine impairs nitric oxide–mediated vasodilation and decreases the production of vasodilator prostacyclin (18).

Many of the above-stated mechanisms apply also to the other commonly used calcineurin-inhibitor, tacrolimus. However, many clinical studies show that hypertension induced by tacrolimus is less pronounced (19). A switch from cyclosporine to tacrolimus resulted in a decrease in blood pressure in most kidney transplant recipients (20).

In the long run, calcineurin inhibitors, notably cyclosporine, cause interstitial fibrosis and vascular as well as tubular damage in the graft possibly mediated by a common endothelin-TGF $\beta$ 1 pathway (21).

Also, steroid therapy contributes to hypertension in kidney transplant patients. Blood pressure could be linked to both current and cumulative steroid dose (22).

Second, vascular alterations in kidney transplant patients contribute to hypertension. We have shown impaired functional (i.e. disturbed endothelial function and large artery elasticity) and structural wall properties of large arteries (23,24). These atherosclerotic lesions are not induced by kidney transplantation (i.e. exist already before transplantation in patients with end-stage renal disease). Disturbed endothelial function (i.e. nitric oxide–dependent vasodilation) and large artery stiffness

are major determinants of increased pulse pressure, predominantly systolic hypertension and increased cardiac afterload (25).

Third, disease of the graft is a major determinant of hypertension after kidney transplantation. Animal studies document well that hypertension can be acquired by transplantation of a kidney from a hypertensive donor into a normotensive recipient (26). The kidney appears to have an important role in long-term blood pressure regulation, overriding other control mechanisms. The same has been observed in humans. For example, Curtis and co-workers reported remission of hypertension after kidney transplantation from normotensive donors in six hypertensive patients who developed end-stage renal disease due to nephrosclerosis (27). These patients did not receive calcineurin inhibitors.

In patients with primary renal disease, hypertension is common. Even patients with glomerular filtration rates still in the normal range often have elevated blood pressure. Hypertension in patients with renal disease has been shown to be sodium sensitive (28). The severity of hypertension rises with increasing serum creatinine as marker of progressive renal injury (29). This is also true for kidney transplant recipients. Curtis and co-workers demonstrated sodium dependency in renal transplant patients (11). Several authors observed an inverse relationship between blood pressure and graft function in kidney transplant patients (30).

The renal allograft is subject to a number of immunologic (e.g. chronic rejection) and non-immunologic processes (e.g. hyperlipidaemia and impaired glucose metabolism) that cause progressive graft failure and eventually graft loss (31). Besides these factors, also recurrence of the primary renal disease in the graft may contribute to progressive graft failure (32). Examples for renal disease likely to recur in the graft are focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis but also Ig-A nephropathy. As stated above, progressive decline of graft function is associated with increasing blood pressure levels.

Importantly, hypertension and impaired graft function constitute a vicious circle, impaired graft function promoting hypertension and hypertension accelerating chronic graft failure due to both immunologic and non-immunologic causes (33). In this context, transplantation of marginal grafts has to be reconsidered (30). It has been shown that measures to increase the number of functioning nephrons (i.e. double kidney grafting in the case of elderly donors with marginal renal function) may result in well-controlled blood pressure in the recipients (34).

Fourth, the diseased native kidneys, though nonfunctional, may significantly contribute to hypertension in renal transplant patients. With effective antihypertensive treatment available, bilateral native kidney nephrectomy is rarely performed in kidney transplant recipients. However, several studies clearly document lower blood pressure in patients after bilateral native kidney nephrectomy (35). Signals arising in the diseased native kidney seem to be responsible for the blood pressure elevation. Excitation of renal afferent nerves mediates an increase in central sympathetic outflow (36). Even moderate damage of the kidney is sufficient to elicit a sustained increase in sympathetic nerve activity and blood pressure that can be prevented by renal denervation (37). We could show that not uraemia-related toxins but other factors such as local renin release or the activation of mechano- and chemoreceptors by fibroproliferative scarring in the diseased kidneys



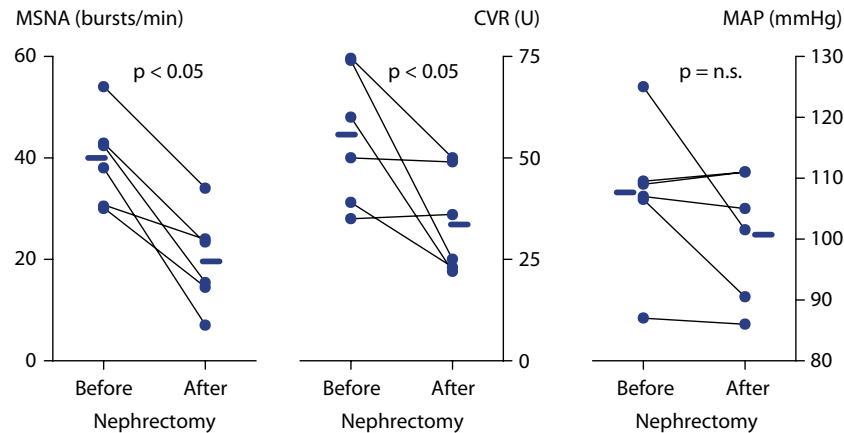


**Figure 60.1** Muscle sympathetic nerve activity (MSNA), calf vascular resistance (CVR) and mean arterial pressure (MAP) in six renal transplant recipients before and after native kidney nephrectomy. Horizontal bars indicate mean values. (Adapted from Hausberg M et al. *Circulation* 2002; 106: 1974–1979, with permission.)

are responsible for sustained sympathetic activation in patients with end-stage renal disease and renal allograft recipients (Figure 60.1) (38).

Fifth, stenosis of the kidney graft artery causes hypertension in 2–7% of renal transplant patients despite technical progress in surgical procedures such as the use of aortic patches and improved perfusion techniques before transplantation (Figure 60.2). Major causes of graft artery stenosis are immunologic factors related to rejection but also infection (e.g. cytomegalovirus infection) and nonimmunologic factors such as hyperlipidaemia (39). Pre-existent atherosclerosis of the graft artery particularly in elderly donors favours the development of hemodynamically relevant stenosis. The risk of developing graft artery stenosis increases with cold ischaemia time. In a survey by Patel et al., the prevalence of kidney graft artery stenosis was 4.1% in recipients from cadaveric donors, contrasting with

0.8% in recipients from living donors (39). Noninvasive techniques such as color-coded Duplex ultrasound or magnetic resonance angiography allow to reliably establish the diagnosis of kidney graft artery stenosis.

Finally, rare causes of hypertension in kidney transplant patients, such as post-transplant erythrocytosis (40) due to unregulated secretion of erythropoietin from the graft, or genetic factors possibly linked to the graft (41), have to be considered.

### IMPACT OF HYPERTENSION IN KIDNEY TRANSPLANT RECIPIENTS

Hypertension is of prognostic relevance for both patient and graft survival. Patients with end-stage renal disease

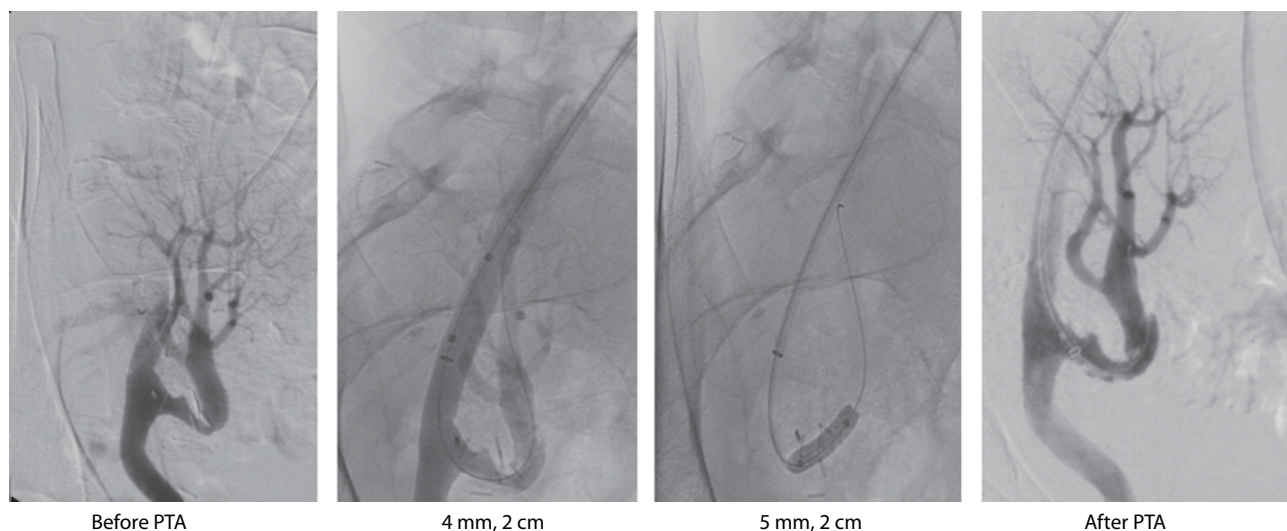


**Figure 60.2** Transplant renal artery stenosis in one patient leading to graft failure and severe hypertension. Graft failure resolved and hypertension improved after successful angioplasty with stenting.



are characterized by a large burden of cardiovascular disease (42). Hypertension in these patients is particularly related to atherosclerotic disease with alterations of large artery elastic wall properties and endothelial function. As summarized by London and co-workers, increased large artery stiffness results in increased cardiac afterload, thus left ventricular hypertrophy, and at the same time reduced diastolic perfusion—both leading to an increased risk of coronary events (43). Structural alterations of large arteries are paralleled by cardiac hypertrophy (25). Indeed, Blacher et al. could demonstrate that increased large artery stiffness is an independent predictor of cardiovascular and overall mortality in patients with end-stage renal disease (44). These issues are not resolved by successful kidney transplantation. McGregor and co-workers could show that echocardiographic abnormalities (i.e. left ventricular hypertrophy) at the time of kidney transplantation predict survival of allograft recipients (45). Our group could show that left ventricular hypertrophy and structural alterations of large arteries persist after kidney transplantation despite effectively treated hypertension (24). Moreover, large artery stiffness measured during the first year after transplantation is an independent factor predicting subsequent cardiovascular morbidity in kidney transplant patients (46). Cardiovascular mortality in kidney transplant patients is approximately four times higher than observed in an age- and sex-matched general population, and hypertension could be identified as a major determinant of the excess mortality (42).

Hypertension is related to endothelial cell injury, although endothelial damage in kidney transplant patients is multifactorial (23). Endothelial injury may be a link between hypertension and progressive graft dysfunction after kidney transplantation. In patients with chronic renal disease of diabetic and nondiabetic origin, hypertension is

a major if not the most important factor determining the progression of renal failure. The same could be demonstrated in kidney transplantation in animal models and in humans. Kidney transplant recipients, particularly those with already impaired graft function, often have an inadequate number of functionally intact nephrons (30). The consequences are hyperfiltration with excessive glomerular protein excretion and subsequent interstitial and glomerular inflammation, and finally scarring, which results in a further reduction of the number of functional nephrons. This vicious circle is accelerated by hypertension which increases glomerular filtration pressure and causes endothelial damage and therefore substantially contributes to enhanced filtration of macromolecules across the capillary barrier (47).

Opelz and co-workers (48) have published an impressive analysis where systolic blood pressure 1 year after transplantation was strongly related to long-term graft survival (Figure 60.3), even when corrected for patients dying with a functioning graft. Importantly, the relation was stronger for systolic than for diastolic or mean arterial pressure. Since systolic blood pressure is better related to functional and structural arterial damage than diastolic or mean blood pressure (49), this suggests that arterial injury predicts kidney graft survival. From the correlation analysis, no definite conclusions can be made as to whether hypertension is a marker or a cause of arterial injury and graft loss in kidney transplant patients. However, several observations suggest that hypertension is a cause of graft loss. First, the above-cited relationship between blood pressure and graft survival was also observed in recipients of living related donors who had excellent human leucocyte antigens (HLA) matching and no rejection episodes, thus who were unlikely to have lost their grafts due to immunologic causes. Second, the outcome of vascular

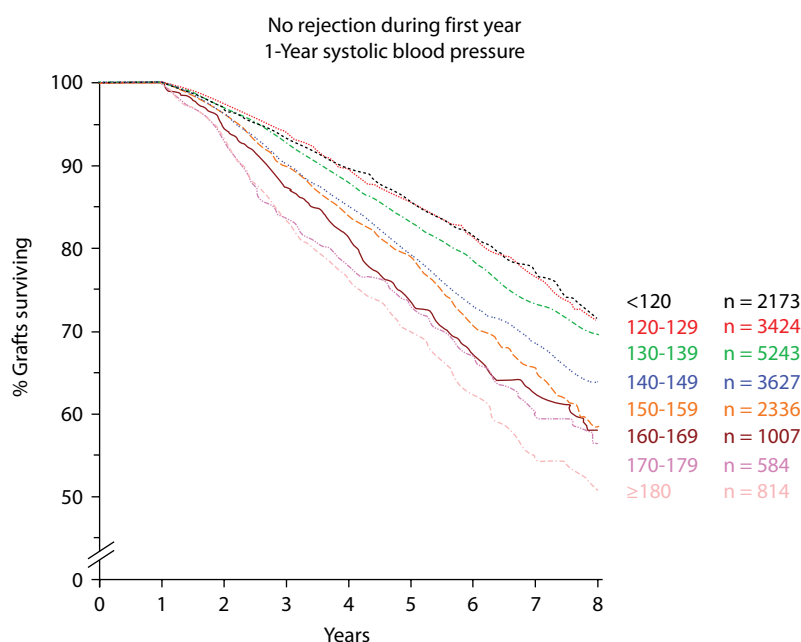


**Figure 60.3** Depicted is kidney graft survival as function of systolic blood pressure 1 year after transplantation. The analysis included only those patients with graft survival of at least 1 year and no rejection episode during the first year after transplantation. (Adapted from Opelz G et al. *Kidney Int* 1998; 53: 217–222, with permission.)

rejection episodes appears to be aggravated by hypertension (50). Third, animal models allow separation of the effects of immunologic factors and hypertension on graft damage and clearly identify hypertension as cause of kidney graft loss (51). From the available observations, we suggest that target blood pressure for hypertensive kidney transplant recipients (but also for other solid organ transplant recipients) should be less than 130/80 mmHg. This is supported by current KDIGO guidelines (52) and also from current guidelines on target blood pressure in hypertensive patients with high cardiovascular risk (53,54)—present in the majority of solid organ transplant recipients.

## ANTIHYPERTENSIVE THERAPY IN KIDNEY TRANSPLANT RECIPIENTS

Early studies demonstrated the sodium-dependency of hypertension in kidney transplant recipients (11). This concept has proven true to date. Diuretics are effective antihypertensive drugs after kidney transplantation, and they are particularly useful in patients with impaired graft function (55). Beta-blockers have also been proven effective.

In the 1990s, calcium channel blockers were recognized as very effective drugs for the treatment of hypertension in renal transplant patients. They combine vasodilating with natriuretic properties, lower blood pressure substantially and counteract cyclosporine-induced hypoperfusion (56). Therefore, they can be expected to exert some nephroprotective action after renal transplantation. Rahn et al. (57) evaluated the effects of the calcium antagonist nitrendipine on graft function in renal transplant patients receiving cyclosporine during an observation period of 2 years. Indeed, they observed a protective effect of nitrendipine on graft function which was independent of the blood pressure-lowering effect.

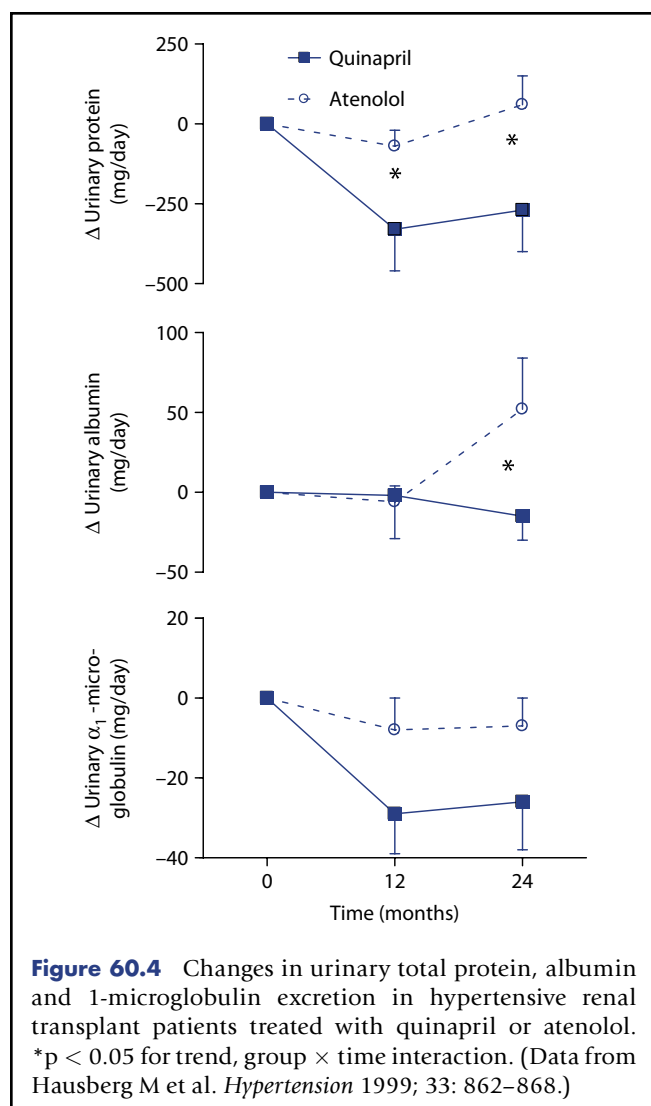
Initially, ACE inhibitors were only administered to a relatively small proportion of renal transplant patients and used with great caution. Indeed, several reports exist on acute renal failure in renal transplant recipients after administration of ACE inhibitors. In some cases, this was attributable to renal artery stenosis of the graft (58). Ahmad et al. observed serious impairment of graft function induced by captopril in renal transplant patients receiving cyclosporine even in the absence of renal artery stenosis (59). Also, Murray et al. observed enalapril-associated acute graft failure in cyclosporine-treated kidney transplant recipients (60). This phenomenon could be explained by additive adverse effects of cyclosporine and ACE inhibitors on glomerular hemodynamics with a subsequent substantial decrease in glomerular filtration pressure.

However, several recent trials could prove the effectiveness and safety of ACE inhibitors after kidney transplantation.

Several studies compared the effects of calcium channel blockers with those of ACE inhibitors in renal transplant patients. Mourad et al. (61), van der Schaaf et al. (62), Sennesael et al. (63), Curtis et al. (64) and Abu-Romeh et al. (65) compared the effects of an ACE inhibitor with those of a calcium antagonist in cyclosporine-treated renal transplant patients. None of these studies showed adverse effects for the ACE inhibitors. Mourad et al. showed after a treatment period of 30 months a similar degree of renal protection and reduction of arterial pressure with lisinopril and nifedipine (61). Van der Schaaf et al. found

amlodipine to have a more pronounced antihypertensive effects than lisinopril in renal allograft recipients (62). Glomerular filtration rate increased with amlodipine, whereas it remained unchanged during lisinopril treatment. In this crossover study, patients were treated for 2 months with each drug. In a similar crossover design, Sennesael et al. compared perindopril and amlodipine in 10 renal allograft recipients and found no significant differences in blood pressure reduction or renal function (63). Curtis et al. (64) and Abu-Romeh et al. (65) both showed a slight decrease in glomerular filtration rate with the ACE inhibitor but not with the calcium antagonist. However, these two studies comprised only treatment periods of less than 1 month. Grekas et al. showed that combination therapy of a calcium antagonist with an ACE inhibitor in renal allograft recipients for 2 months results in superior blood pressure control, reduction in proteinuria and no significant change in glomerular filtration rate when compared to antihypertensive therapy with a calcium antagonist alone (66). Taken together, ACE inhibitors appear as effective as calcium antagonists with regard to blood pressure reduction and preservation of graft function. The effects of the ACE inhibitor quinapril and those of the beta-blocker atenolol on blood pressure and graft function were compared in cyclosporine-treated hypertensive kidney transplant recipients (67). Quinapril and atenolol were equally effective in the treatment of post-transplant hypertension in renal allograft recipients. Renal transplant function did not differ between patients treated with quinapril and with atenolol. In neither group could a significant deterioration of renal allograft function be observed at the end of the 24 months' treatment period. However, when compared to the changes in the atenolol group, quinapril-treated renal allograft recipients showed a significant reduction of proteinuria and urinary albumin excretion at the end of the 24 months' observation period (Figure 60.4).

From these studies, it appears that ACE inhibitors are equally effective but apparently not better than other classes of antihypertensive drugs such as calcium channel blockers or beta-blockers with regard to the preservation of allograft function in hypertensive kidney transplant patients. However, a major limitation of all these studies is a relatively short observation period. ACE inhibitors but not the other antihypertensive drugs unequivocally showed a reduction in proteinuria. Therefore, it is conceivable that after a longer observation period beneficial effects of ACE inhibitors—and possibly angiotensin receptor blockers—as compared to other classes of antihypertensive drugs may appear with respect to graft function. In favour of this argues the following: First, a progressive decline in graft function was found to correlate with the amount of protein excreted in the urine (31,33). Hohage et al. observed a negative influence of even mild proteinuria (less than 1 g per day, Figure 60.5) on long-term graft survival in renal transplant patients (68). Second, Barnas et al. observed a beneficial effect of the ACE inhibitor lisinopril on graft function in those renal transplant patients with chronic allograft dysfunction in whom proteinuria decreased after initiation of ACE inhibitor treatment (69). Third, in many large studies on the effects of ACE inhibitors on the progression of chronic renal disease, reduction of proteinuria precedes and consistently correlates with the nephroprotective effect (70,71). Reduction of proteinuria was observed early, a significant benefit of ACE inhibitors on the course of renal function that often appeared



only after 2 years of treatment. This is consistent with the idea that excessive glomerular protein filtration leads to increased reabsorption in the proximal tubulus with subsequent perinuclear organelle overload and upregulation of vasoactive and inflammatory genes. These processes contribute to tubulo-interstitial injury and scarring (72). Genetic variants of the renin–angiotensin system in renal transplant recipients may contribute to the rate of progression of chronic graft nephropathy (73).

Fourth, two retrospective studies suggest a beneficial effect of ACE-inhibitors and angiotensin receptor blockers on graft survival in renal transplant recipients. Heinze and co-workers observed a 10-year graft survival rate of 59% in ACEI/ARB users versus 41% in nonusers ( $p < 0.001$ ) (74). However, functional graft survival (adjusted for death with functioning graft) did not differ between groups in that study. We observed significantly increased functional graft survival in renal transplant patients receiving long-term treatment (>2 years) with ACE-inhibitors or angiotensin receptor blockers, particularly when combined with calcium antagonists (75).

When considering specific advantages of individual classes of antihypertensive drugs, it has to be considered that hypertension in kidney transplant recipients

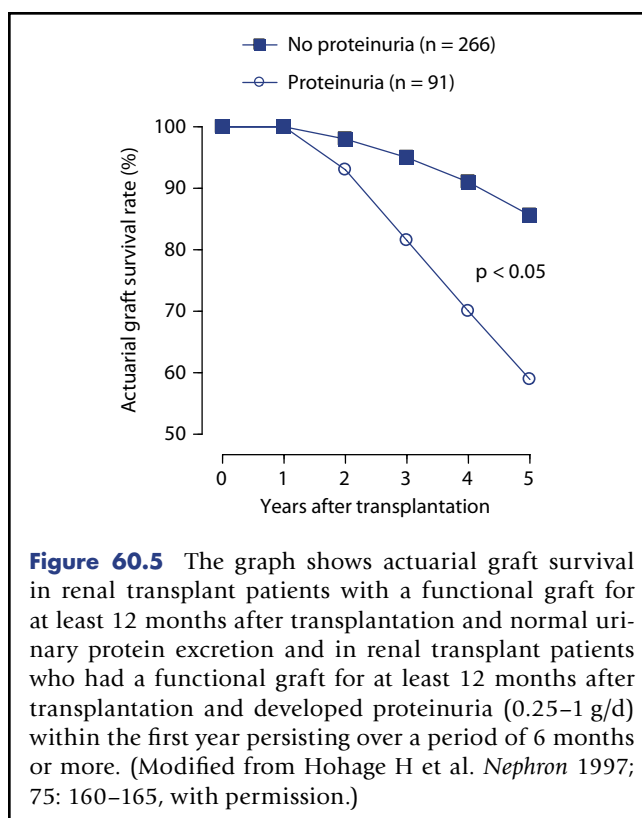


**Figure 60.5** The graph shows actuarial graft survival in renal transplant patients with a functional graft for at least 12 months after transplantation and normal urinary protein excretion and in renal transplant patients who had a functional graft for at least 12 months after transplantation and developed proteinuria (0.25–1 g/d) within the first year persisting over a period of 6 months or more. (Modified from Hohage H et al. *Nephron* 1997; 75: 160–165, with permission.)

is generally severe, especially when calcineurin inhibitors are used. Combination of multiple antihypertensive drugs is required for adequate blood pressure control, for example, combination of a diuretic, a calcium antagonist and an ACE inhibitor or beta-blocker.

Studies investigating calcineurin inhibitor withdrawal after kidney transplantation are under way. Some reports clearly demonstrate a pronounced decrease in blood pressure after discontinuation of calcineurin inhibitors (76,77). However, calcineurin inhibitor withdrawal may also negatively affect graft survival since associated with a higher rate of late chronic antibody-mediated rejection (78,79).

## CONCLUSIONS

Hypertension is common in solid organ transplant recipients, especially with the use of modern immunosuppressive drugs such as cyclosporine. In kidney transplant recipients, hypertension is of major prognostic relevance for graft survival but also for the incidence of cardiovascular events. Also, in nonrenal solid organ transplant recipients, hypertension emerges as a significant prognostic factor. Effective antihypertensive therapy is mandatory, and is possible by combinations of different classes of antihypertensive drugs.

## REFERENCES

1. Myers J. Clinical and exercise test determinants of survival after cardiac transplantation. *Chest* 2003; 124: 2000–2005.
2. Guckelberger O, Mutzke F, Glanemann M et al. Validation of cardiovascular risk scores in a liver transplant population. *Liver Transpl* 2006; 12: 394–401.

3. Ojo AO, Held PJ, Port FK et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003; 349: 931–940.
4. European Multicentre Trial G. Cyclosporin in cadaveric renal transplantation: One-year follow-up of a multicentre trial. *Lancet* 1983; 2: 986–989.
5. Fontan M P, Rodriguez-Carmona A, Garcia Falcon T et al. Early immunologic and nonimmunologic predictors of arterial hypertension after renal transplantation. *Am J Kidney Dis* 1999; 33: 21–28.
6. Schwenger V, Zeier M, Ritz E. Hypertension after renal transplantation. *Curr Hypertens Rep* 2001; 3: 434–439.
7. Scherrer U, Vissing SF, Morgan BJ et al. Cyclosporine-induced sympathetic activation and hypertension after heart transplantation. *N Engl J Med* 1990; 323: 693–699.
8. Canzanella VJ, Textor SC, Taler SJ et al. Late hypertension after liver transplantation: A comparison of cyclosporine and tacrolimus (FK 506). *Liver Transpl Surg* 1998; 4: 328–334.
9. Stein CM, He H, Pincus T, Wood AJ. Cyclosporine impairs vasodilation without increased sympathetic activity in humans. *Hypertension* 1995; 26: 705–710.
10. Curtis JJ, Luke RG, Dubovsky E et al. Cyclosporin in therapeutic doses increases renal allograft vascular resistance. *Lancet* 1986; 2: 477–479.
11. Curtis JJ, Luke RG, Jones P, Diethelm AG. Hypertension in cyclosporine-treated renal transplant recipients is sodium dependent. *Am J Med* 1988; 85: 134–138.
12. Julien J, Farge D, Kreft-Jais C et al. Cyclosporine-induced stimulation of the renin-angiotensin system after liver and heart transplantation. *Transplantation* 1993; 56: 885–891.
13. Darlametsos IE, Varonos DD. Role of prostanoids and endothelins in the prevention of cyclosporine-induced nephrotoxicity. *Prostaglandins Leukot Essent Fatty Acids* 2001; 64: 231–239.
14. Lyson T, Ermel LD, Belshaw PJ et al. Cyclosporine- and FK506-induced sympathetic activation correlates with calcineurin-mediated inhibition of T-cell signaling. *Circ Res* 1993; 73: 596–602.
15. Rundqvist B, Elam M, Eisenhofer G, Friberg P. Normalization of total body and regional sympathetic hyperactivity in heart failure after heart transplantation. *J Heart Lung Transplant Off Publ Int Soc Heart Transplant* 1996; 15: 516–526.
16. Hausberg M, Lang D, Levers A et al. Sympathetic nerve activity in renal transplant patients before and after withdrawal of cyclosporine. *J Hypertens* 2006; 24: 957–964.
17. Zhang W, Li JL, Hosaka M et al. Cyclosporine A-induced hypertension involves synapsin in renal sensory nerve endings. *Proc Natl Acad Sci USA* 2000; 97: 9765–9770.
18. Gossmann J, Radounikl A, Bernemann A et al. Pathophysiology of cyclosporine-induced nephrotoxicity in humans: A role for nitric oxide? *Kidney Blood Press Res* 2001; 24: 111–115.
19. Vincenti F, Jensik SC, Filo RS et al. A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: Evidence for improved allograft survival at five years. *Transplantation* 2002; 73: 775–782.
20. Friemann S, Feuring E, Padberg W, Ernst W. Improvement of nephrotoxicity, hypertension, and lipid metabolism after conversion of kidney transplant recipients from cyclosporine to tacrolimus. *Transplant Proc* 1998; 30: 1240–1242.
21. Vanrenterghem YF. Which calcineurin inhibitor is preferred in renal transplantation: Tacrolimus or cyclosporine? *Curr Opin Nephrol Hypertens* 1999; 8: 669–674.
22. Taler SJ, Textor SC, Canzanella VJ et al. Role of steroid dose in hypertension early after liver transplantation with tacrolimus (FK506) and cyclosporine. *Transplantation* 1996; 62: 1588–1592.
23. Hausberg M, Kisters K, Kosch M et al. Flow-mediated vasodilation and distensibility of the brachial artery in renal allograft recipients. *Kidney Int* 1999; 55: 1104–1110.
24. Suwelack B, Witta J, Hausberg M et al. Studies on structural changes of the carotid arteries and the heart in asymptomatic renal transplant recipients. *Nephrol Dial Transplant* 1999; 14: 160–165.
25. London GM, Guerin AP, Marchais SJ et al. Cardiac and arterial interactions in end-stage renal disease. *Kidney Int* 1996; 50: 600–608.
26. Rettig R. Does the kidney play a role in the aetiology of primary hypertension? Evidence from renal transplantation studies in rats and humans. *J Hum Hypertens* 1993; 7: 177–180.
27. Curtis JJ, Luke RG, Dustan HP et al. Remission of essential hypertension after renal transplantation. *N Engl J Med* 1983; 309: 1009–1015.
28. Brod J, Schaeffer J, Hengstenberg JH, Kleinschmidt TG. Investigations on the Na<sup>+</sup>, K<sup>+</sup>-pump in erythrocytes of patients with renal hypertension. *Clin Sci (London)* 1984; 66: 351–355.
29. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure. Less of one, more the other? *Am J Hypertens* 1988; 1: 335–347.
30. Brenner BM, Milford EL. Nephron underdosing: A programmed cause of chronic renal allograft failure. *Am J Kidney Dis* 1993; 21: 66–72.
31. Kasiske BL, Heim-Duthoy KL, Tortorice KL, Rao KV. The variable nature of chronic declines in renal allograft function. *Transplantation* 1991; 51: 330–334.
32. Michielsen P. Recurrence of the original disease. Does this influence renal graft failure? *Kidney Int Suppl* 1995; 52: S79–S84.
33. Massy ZA, Guijarro C, Wiederkehr MR et al. Chronic renal allograft rejection: Immunologic and nonimmunologic risk factors. *Kidney Int* 1996; 49: 518–524.
34. Remuzzi G, Grinyo J, Ruggenenti P et al. Early experience with dual kidney transplantation in adults using expanded donor criteria. Double Kidney Transplant Group (DKG). *J Am Soc Nephrol* 1999; 10: 2591–2598.
35. Curtis JJ, Luke RG, Diethelm AG et al. Benefits of removal of native kidneys in hypertension after renal transplantation. *Lancet* 1985; 2: 739–742.
36. Campese VM, Kogosov E. Renal afferent denervation prevents hypertension in rats with chronic renal failure. *Hypertension* 1995; 25: 878–882.
37. Ye S, Gamburd M, Mozayani P, Koss M, Campese VM. A limited renal injury may cause a permanent form of neurogenic hypertension. *Am J Hypertens* 1998; 11: 723–728.
38. Hausberg M, Kosch M, Harmelink P et al. Sympathetic nerve activity in end-stage renal disease. *Circulation* 2002; 106: 1974–1979.
39. Patel NH, Jindal RM, Wilkin T et al. Renal arterial stenosis in renal allografts: Retrospective study of predisposing factors and outcome after percutaneous transluminal angioplasty. *Radiology* 2001; 219: 663–667.
40. Gaston RS, Julian BA, Curtis JJ. Posttransplant erythrocytosis: An enigma revisited. *Am J Kidney Dis* 1994; 24: 1–11.
41. Guidi E, Menghetti D, Milani S et al. Hypertension may be transplanted with the kidney in humans: A long-term historical prospective follow-up of recipients grafted with kidneys coming from donors with or without hypertension in their families. *J Am Soc Nephrol* 1996; 7: 1131–1138.
42. Kasiske BL, Guijarro C, Massy ZA et al. Cardiovascular disease after renal transplantation. *J Am Soc Nephrol* 1996; 7: 158–165.
43. London GM, Drueke TB. Atherosclerosis and arteriosclerosis in chronic renal failure. *Kidney Int* 1997; 51: 1678–1695.
44. Blacher J, Guerin AP, Pannier B et al. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999; 99: 2434–2439.
45. McGregor E, Jardine AG, Murray LS et al. Pre-operative echocardiographic abnormalities and adverse outcome following renal transplantation. *Nephrol Dial Transplant* 1998; 13: 1499–1505.
46. Barenbrock M, Kosch M, Jöster E et al. Reduced arterial distensibility is a predictor of cardiovascular disease in patients after renal transplantation. *J Hypertens* 2002; 20: 79–84.
47. Ruggenenti P, Remuzzi G. The role of protein traffic in the progression of renal diseases. *Annu Rev Med* 2000; 51: 315–327.
48. Opelz G, Wujciak T, Ritz E. Association of chronic kidney graft failure with recipient blood pressure. Collaborative Transplant Study. *Kidney Int* 1998; 53: 217–222.
49. Safar M, Blacher J, Mourad J, London G. Stiffness of carotid artery wall material and blood pressure in humans: Application to antihypertensive therapy and stroke prevention. *Stroke* 2000; 31: 782–790.
50. Cosio FG, Pelletier RP, Pesavento TE et al. Elevated blood pressure predicts the risk of acute rejection in renal allograft recipients. *Kidney Int* 2001; 59: 1158–1164.
51. Schindler R, Tanriver Y, Frei U. Hypertension and allograft nephropathy—cause, consequence, or both? *Nephrol Dial Transplant* 2000; 15: 8–10.
52. Kasiske B, Wheeler D. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney Int Suppl* 2012; 2: 337–414.
53. Krämer BK, Hausberg M, Sanner B et al. für die Task Force Wissenschaftliche Stellungnahmen und Leitlinien der DHL®. [Blood Pressure Measurement and Treatment Targets: Position Paper of the DHL® Task Force Scientific Statements and Guidelines]. *Dtsch Med Wochenschr* 2017; 142: 1446–1447.
54. Whelton PK, Carey RM, Aronow WS et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high



- blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Hypertension* 2018 June; 71(6): 1269–1324.
55. Curtis JJ. Management of hypertension after transplantation. *Kidney Int Suppl* 1993; 43: S45–S49.
  56. Ruggenenti P, Perico N, Mosconi L et al. Calcium channel blockers protect transplant patients from cyclosporine-induced daily renal hypoperfusion. *Kidney Int* 1993; 43: 706–711.
  57. Rahn KH, Barenbrock M, Fritschka E et al. Effect of nitrendipine on renal function in renal-transplant patients treated with cyclosporin: A randomised trial. *Lancet* 1999; 354: 1415–1420.
  58. Curtis JJ, Luke RG, Whelchel JD et al. Inhibition of angiotensin-converting enzyme in renal-transplant recipients with hypertension. *N Engl J Med* 1983; 308: 377–381.
  59. Ahmad T, Coulthard MG, Eastham EJ. Reversible renal failure due to the use of captopril in a renal allograft recipient treated with cyclosporin. *Nephrol Dial Transplant* 1989; 4: 311–312.
  60. Murray BM, Venuto RC, Kohli R, Cunningham EE. Enalapril-associated acute renal failure in renal transplants: Possible role of cyclosporine. *Am J Kidney Dis* 1990; 16: 66–69.
  61. Mourad G, Ribstein J, Mimran A. Converting-enzyme inhibitor versus calcium antagonist in cyclosporine-treated renal transplants. *Kidney Int* 1993; 43: 419–425.
  62. van der Schaaf MR, Hené RJ, Floor M et al. Hypertension after renal transplantation. Calcium channel or converting enzyme blockade? *Hypertension* 1995; 25: 77–81.
  63. Sennesael J, Lamote J, Violet I et al. Comparison of perindopril and amlodipine in cyclosporine-treated renal allograft recipients. *Hypertension* 1995; 26: 436–444.
  64. Curtis JJ, Laskow DA, Jones PA et al. Captopril-induced fall in glomerular filtration rate in cyclosporine-treated hypertensive patients. *J Am Soc Nephrol* 1993; 3: 1570–1574.
  65. Abu-Romeh SH, el-Khatib D, Rashid A et al. Comparative effects of enalapril and nifedipine on renal hemodynamics in hypertensive renal allograft recipients. *Clin Nephrol* 1992; 37: 183–188.
  66. Grekas D, Dioudis C, Kalevosoglou I et al. Renal hemodynamics in hypertensive renal allograft recipients: Effects of calcium antagonists and ACE inhibitors. *Kidney Int Suppl* 1996; 55: S97–100.
  67. Hausberg M, Barenbrock M, Hohage H et al. ACE inhibitor versus beta-blocker for the treatment of hypertension in renal allograft recipients. *Hypertension* 1999; 33: 862–868.
  68. Hohage H, Kleyer U, Bruckner D et al. Influence of proteinuria on long-term transplant survival in kidney transplant recipients. *Nephron* 1997; 75: 160–165.
  69. Barnas U, Schmidt A, Haas M et al. The effects of prolonged angiotensin-converting enzyme inhibition on excretory kidney function and proteinuria in renal allograft recipients with chronic progressive transplant failure. *Nephrol Dial Transplant* 1996; 11: 1822–1824.
  70. Maschio G, Alberti D, Janin G et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N Engl J Med* 1996; 334: 939–945.
  71. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet* 1997; 349: 1857–1863.
  72. Bruzzi I, Benigni A, Remuzzi G. Role of increased glomerular protein traffic in the progression of renal failure. *Kidney Int Suppl* 1997; 62: S29–S31.
  73. Sharma AM, Beige J, Distler A. Role of genetic variants of the renin-angiotensin system in chronic renal allograft injury. *Kidney Int* 1998; 53: 1461–1465.
  74. Heinze G, Mitterbauer C, Regele H et al. Angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal transplantation. *J Am Soc Nephrol* 2006; 17: 889–899.
  75. Hausberg M, Loley K, Levers A et al. Influence of blood pressure and antihypertensive treatment on graft survival after kidney transplantation. *J Hypertens* 2005; 23: S4–S4.
  76. Schnuelle P, van der Heide JH, Tegzess A et al. Open randomized trial comparing early withdrawal of either cyclosporine or mycophenolate mofetil in stable renal transplant recipients initially treated with a triple drug regimen. *J Am Soc Nephrol* 2002; 13: 536–543.
  77. Johnson RW, Kreis H, Oberbauer R et al. Sirolimus allows early cyclosporine withdrawal in renal transplantation resulting in improved renal function and lower blood pressure. *Transplantation* 2001; 72: 777–786.
  78. Karpe KM, Talaulikar GS, Walters GD. Calcineurin inhibitor withdrawal or tapering for kidney transplant recipients. *Cochrane Database Syst Rev* 2017; 7: CD006750.
  79. Tabibzadeh N, Glowacki F, Frimat M et al. Long-term outcome after early cyclosporine withdrawal in kidney transplantation: Ten years after. *Clin Transplant* 2016; 30: 1480–1487.



# Section IX

## Secondary Hypertension: Diagnosis and Treatment

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*Peter W. de Leeuw and Alberto Morganti*

## INTRODUCTION

In most hypertensive patients, no cause for the elevated blood pressure (BP) is apparent. In such cases, hypertension is being labelled as 'primary' or 'essential', even when some pathophysiological mechanism (e.g. sympathetic overactivity or sodium sensitivity) seems to prevail in the pathogenesis of the disorder. The term 'secondary hypertension' is reserved for those conditions in which a specific underlying disease is responsible for the abnormal BP. One of the most frequent causes of secondary hypertension is renovascular hypertension (RVH) due to renal artery stenosis (RAS). Since this abnormality is potentially curable, the clinician needs to remain alert for certain signs and symptoms which could raise suspicion of RVH, even though the absence of such signs does not always rule out the condition.

Notwithstanding the attempts of some earlier experimenters, Goldblatt and co-workers were the first to recognize renal arterial narrowing as a cause of hypertension (1). They performed several experiments in dogs to test the hypothesis that 'ischaemia limited to the kidneys may be the initial condition in the pathogenesis of the hypertension that is associated with nephrosclerosis'. They reasoned that, if this hypothesis was correct, renal ischaemia from whatever cause would be followed by a rise in BP. With a specifically designed clamp, the investigators induced variable degrees of renal artery obstruction and, indeed, found substantial increases in systolic pressure. Unilateral clamping already caused a moderate rise in pressure, but pressure rose to very high levels following the production of bilateral ischaemia (1). Although renin as a pressor substance of renal origin had already been discovered nearly 40 years earlier (2), it did not occur to Goldblatt and his co-workers that this substance could be the mediator of their renal ischaemia-related type of hypertension. The second half of the twentieth century, however, saw a tremendous boost in renin research and it soon became apparent that the renin-angiotensin system (RAS) is critically involved in the development of hypertension secondary to renal artery clipping (3). Meanwhile, RVH had also been identified in man with the notion that relief of the renal artery constriction or excision of the kidney distal to the stenotic artery could lower the pressure (3). In clinical practice,

however, it may sometimes be difficult to differentiate a renovascular origin of hypertension from other causes. For instance, in patients with post-transplant hypertension, a rise in BP may be secondary to a combination of RAS, parenchymal damage and the effects of immunosuppressive therapy. In the present chapter, we focus on 'isolated' renovascular abnormalities as the cause of hypertension. The most important causes of such abnormalities are atherosclerosis and fibromuscular dysplasia (FMD). Examples of these are presented in [Figure 61.1](#).

## EPIDEMIOLOGY OF RENOVASCULAR DISEASE

Precise figures on the prevalence of RAS in the normal population are lacking. This is largely so because making a definite diagnosis of RAS requires either invasive techniques and/or the use of contrast agents. Therefore, prevalence studies can only be performed in populations with an already high likelihood of having the abnormality. Perhaps the best way to get an estimate of the prevalence of RAS in an unselected population is to assess how often this condition is seen in potential kidney donors. For instance, in a sample of 1957 living donors, Lorenz and co-workers reported a prevalence of 5.3% for atherosclerotic RAS (ARAS) (4). This group, however, comprised both normotensive and hypertensive individuals; differences between these two were not reported. Moreover, the diagnosis of ARAS was based on computed tomographic angiography (CTA) rather than the classical digital subtraction angiography (DSA). There are no studies on the prevalence of DSA-proven ARAS in the general hypertensive population but there are in several other groups. In a meta-analysis of 40 studies involving a total number of 15,879 patients, De Mast and Beutler found an overall prevalence of ARAS of 15.4% in patients who underwent angiographic studies for a variety of reasons (5). As shown in [Table 61.1](#), prevalence increased from 10.5% in unselected patients scheduled for coronary angiography to 54.1% in patients with congestive heart failure. Interestingly, ARAS is found in only one-fifth or less of all hypertensive patients in whom one may suspect this abnormality. It is interesting, therefore, that the

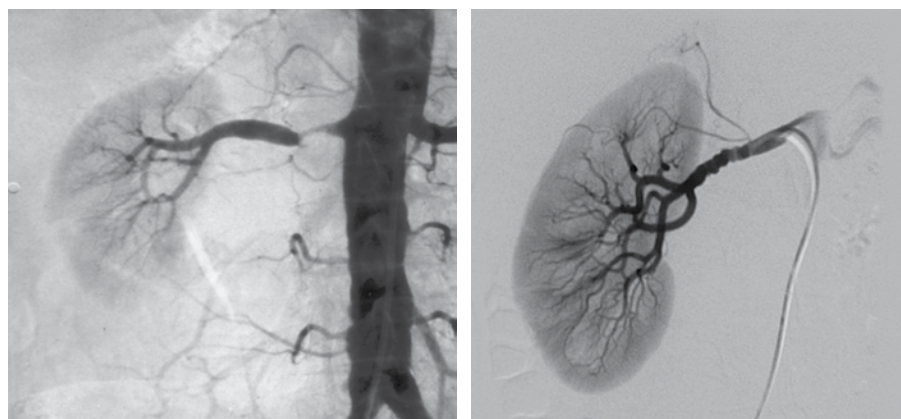


**Figure 61.1** Examples of atherosclerotic renal artery stenosis (left) and fibromuscular dysplasia (right).

**Table 61.1** Prevalence of renal artery stenosis in various risk groups

| Risk group                                | Prevalence                   |
|-------------------------------------------|------------------------------|
| Suspected renovascular hypertension       | 14.1% [12.7–15.8%; n = 1931] |
| Hypertension plus diabetes                | 20.0% [14.9–25.1%; n = 240]  |
| CAG (consecutive patients)                | 10.5% [9.8–11.2%; n = 8011]  |
| CAG (hypertensives only)                  | 17.8% [15.4–20.6%; n = 836]  |
| CAG (plus suspected renovascular disease) | 16.6% [14.8–18.5%; n = 1576] |
| Congestive heart failure                  | 54.1% [45.7–62.3%; n = 135]  |
| Peripheral vascular disease               | 25.3% [23.6–27.0%; n = 2632] |
| Abdominal aortic aneurysm                 | 33.1% [27.4–39.2%; n = 239]  |
| End-stage renal failure                   | 40.8% [27–55.8%; n = 49]     |

Source: Data taken from de Mast Q, Beutler JJ. *J Hypertens* 2009; 27(7): 1333–40.

Note: Between brackets: 95% confidence intervals and sample size of groups.

Abbreviation: CAG, coronary angiography.

chance of finding ARAS is the least in patients in whom one expects this the most. However, in a large epidemiological study evaluating more than one million subjects aged 67 years or older, 50% of whom were hypertensive, the estimated incidence of ARAS was 3.7 per million patient years, with the likelihood of developing the disease being more than doubled in patients with concomitant chronic kidney disease (CKD) and peripheral or coronary atherosclerotic disease (6).

Renal FMD is the non-atheromatous, non-inflammatory counterpart of ARAS and in 85% of cases is due to medial hyperplasia of small and medium size arteries. As for ARAS, the prevalence of FMD is unknown since the disease is very often asymptomatic or discovered incidentally. Since hypertension is, by far, the clinical sign that most frequently raises the suspicion of RAS, studies

addressing the prevalence of FMD were also preferentially carried out in hypertensive patients or in renal donor populations. Among the 997 individuals participating in the CORAL Study, 58 (5.8%) were found to have renal FMD (7), whereas in a meta-analysis of six studies encompassing more than 4000 candidates for kidney donation, the prevalence of FMD varied from 2.3–6.6% (8). It is of note that in these latter studies only 30% of the persons were hypertensive. FMD is a proteiform disease in that the typical multifocal (string of beads) and unifocal stenoses are associated in about 40% of cases with other vascular malformations such as aneurysms or dissections (9). Also, FMD often turns out to be a multivessel rather than a single-vessel disease. From the two largest available registries of FMD, it appears that in about half of the cases two or more vessels are affected, the renal and cervicocephalic vascular districts being the most frequent localization of the disease (10,11). This notion has practical implications since subjects harbouring FMD should always undergo an extensive vascular investigation to reveal the possible multiple sites of the disease.

## RENAL ARTERY STENOSIS VERSUS RENOVASCULAR HYPERTENSION

When ARAS or renal FMD is present in a hypertensive patient, this does not necessarily mean that the lesion is responsible for an elevation of BP. Surely, when BP normalizes after mechanical treatment of the stenotic lesion(s), it is very likely that the patient had RVH. However, in most cases, hypertension either does not change or, at best, is easier to treat after such a procedure. Under those circumstances, RVH may still have been present, but secondary changes in the vasculature prevent BP from falling towards normal levels. Alternatively, RVH may have been superimposed on pre-existing essential hypertension. Hence, RVH can only be diagnosed with certainty in retrospect and even then, in a limited number of patients only. In many cases, therefore, the clinician remains in doubt about whether RAS is responsible for hypertension or not.

Whereas in the case of ARAS it may be difficult to decide which comes first, the stenosis or the hypertension, at first sight the sequence of events seems to be more clear-cut

in patients with renal FMD. However, it remains possible that a patient has essential hypertension with FMD being an 'innocent' bystander. Assuming that patients with 'true' RVH are those in whom BP is normalized after correction of RAS, it was already clear from early studies that the prevalence of RVH was rather low in patients with ARAS, varying from 6–19% (12–14). Technical improvements in angioplasty did not appreciably change these figures, since in a very recent study the rate of hypertension cure in a cohort of 126 patients (77.2% with ARAS) was 11.1% and 7.9% at 12 months after revascularization when assessed by office and home BP (15). In contrast with ARAS the rate of BP normalization after RAS correction is 30–50% in patients with renal FMD (16).

Finally, we must acknowledge that the presence of a RAS does not always lead to hypertension. Indeed, in the early days unselected autopsy studies already failed to show a relationship between accidentally found RAS and hypertension in a substantial number of cases (17,18). More recently, an autopsy study reported several renal artery lesions which were apparently not suspected on clinical grounds and which were not associated with hypertension during life. In a general population older than 65 years and without renal disease, a prevalence of 6.8% was noted (19). Lastly, there are also clinical studies showing incidental RAS in normotensive patients (20,21).

The opposite is also true in that there are more complications of hypertension in patients with than in patients without RAS. Indeed, in the study by Kalra et al. among patients who were found to have ARAS, there was a threefold increase in new-onset cardiovascular events with respect to the general population (6). In a cross-sectional study comparing patients with and without ARAS, the same authors found that only 5.1% of those with ARAS had normal cardiac structure and function and a significantly greater cardiovascular morbidity (22). In addition, in patients with renal FMD the prevalence of atherosclerotic plaques in carotid arteries was greater than in controls matched for BP level and hypertension duration (23). Therefore, the relationship between RAS and hypertension remains enigmatic, and perhaps the idea should be entertained that RAS may exert detrimental cardiovascular effects also via mechanisms not related to BP elevation (24).

## **PATHOPHYSIOLOGICAL CONSIDERATIONS**

Basic concepts in the pathophysiology of RAS take a reduction in renal blood flow as the starting point. Since blood flow to any tissue depends heavily on perfusion pressure, such as the pressure gradient across the organ, one would assume that, at least in theory, renal blood flow will not be affected until the stenosis is so tight that perfusion pressure has become too low. Early observations in experimental animals suggested that the renal arterial luminal diameter must be reduced by at least 70–80% before measurable reductions in perfusion pressure and blood flow develop (25). However, what happens to a kidney with a stenotic artery depends not only on the degree of the stenosis, but also on how acutely this develops, and on the autoregulatory potential of the organ. Most of our knowledge on the sequence of events comes from animal experiments in which RAS was produced by placing a clip or an

inflatable cuff around the vessel. Initially, when the pressure distal to the stenosis is still within the autoregulatory range, intrarenal vasodilation will ensure that renal blood flow is maintained and as long as intraglomerular pressure remains sufficiently high to guarantee an adequate glomerular filtration rate (GFR), the kidney may still function properly. Nevertheless, due to the intrarenal vasodilation the pressure distal to the stenosis will fall further so that the transstenotic pressure gradient will increase. This creates, as it were, a tighter stenosis, and because less of the systemic pressure is now transmitted to the glomeruli, GFR may be jeopardized. However, the lower pressure at the level of the juxtaglomerular apparatus will also stimulate the RAS which in turn raises postglomerular resistance, thereby maintaining glomerular filtration. Angiotensin II also acts on other (dilated) vessels to raise renal vascular resistance to the extent that distal renal artery pressure is restored as much as possible so that the stenosis effect is attenuated (26,27). The restoration of poststenotic pressure and/or renal vascular resistance then shuts off further renin stimulation (27). It follows that the functional impact of a renal artery stenosis, or for that matter the hemodynamic significance of it, largely depends on the resistance to flow in the distal renal vasculature. The competition between the autoregulatory mechanisms favouring vasodilation and the vasoconstrictor action of angiotensin II appears to be most conspicuous with relatively mild degrees of stenosis that are not confounded by significant changes in systemic pressure.

More severe forms of stenosis will produce a longer-lasting stimulation of the RAS and hypertension. To preserve GFR as much as possible, efferent vascular resistance will also be enhanced. Consequently, hydrostatic pressure in the peritubular capillaries falls, which promotes sodium reabsorption. In addition, the activation of the renin system will lead to secondary stimulation of aldosterone. The latter contributes to enhanced retention of sodium of water by the stenotic kidney and to the loss of potassium. If sufficient volume expansion ensues, this reduces renin again, so that eventually a complex interplay between hemodynamic and volume factors keeps the pressure at a high level. When the stenosis becomes so tight that even a substantial rise in systemic pressure cannot overcome the resistance, the kidney will face progressive ischaemia with loss of tissue and severe functional impairment. At the later stages of (experimental) renal artery stenosis, the renin system has no major role anymore in the elevation of BP and is hypertension-sustained by other, less well-understood mechanisms such as enhanced sympathetic activity and vascular hypertrophy. Only when the hypertension evolves into the malignant phase does BP again become renin-dependent.

It should be emphasized that the pathophysiology as outlined above has been derived from experimental situations which are only a remote reflection of what happens in humans. Aside from rare acute occlusions of the renal artery, in man ARAS is a progressive disorder which slowly evolves over time (28), and the same is true for FMD (29). This allows the kidney enough time to completely adapt to alterations in flow. Moreover, a wide spectrum of renovascular abnormalities is possible, ranging from mild unilateral disease to severe bilateral stenosis. Even when there is stenosis on only one side, if and how hypertension develops depends on the function of the contralateral kidney. When this contralateral kidney is still fully intact,



it may get rid of the excess volume retained by the other kidney, and it may suppress its own renin release. It is possible, therefore, that under those conditions BP will rise only mildly or not at all. However, once this kidney gets damaged by an elevated BP itself, it will no longer be able to compensate for the disturbed function of the stenotic kidney. The hypertension, which was initially primarily renin-dependent, now becomes increasingly volume-dependent. Such a volume dependency also dominates the clinical picture when both kidneys are supplied by a stenotic artery.

Another point to consider is that in man, the kidney responds differently to a stenosis caused by atherosclerotic lesions as compared to an FMD-related stenosis. The limited data available suggest that kidneys from patients with FMD are more like those of patients with essential hypertension and not so much prone to reductions in flow as atherosclerotic kidneys (30,31). This corresponds with clinical observations showing that severe renal impairment is common in atherosclerotic renovascular disease but not so much in FMD (10).

Because RAS takes a long time to develop, it is difficult to decide when it has reached hemodynamic significance. One report relating renin release to pressure gradients across the stenosis indicates that such gradients must exceed 10–20 mmHg before renin release is activated (32). However, in this study an acute graded stenosis was superimposed upon an existing stenosis. Moreover, renin responses may have been blunted by concurrent medication. The impact of the stenosis per se remains, therefore, enigmatic.

In addition to the classical 'hemodynamic' understanding of RVH pathophysiology, a number of recent studies, mostly in animals, point to hypoxia as the key player in causing progression of renal damage in the poststenotic kidney (33). Kidneys are highly oxygenated organs, and sufficient oxygenation for physiological functions can be preserved despite some reduction in blood flow in patients with ARAS (34). However, when critical hypoxia develops as a result of long-lasting, severe RAS a number of proinflammatory, prooxidant and profibrinogenic mechanisms are activated, leading to loss and remodelling of renal microvasculature, tubulointerstitial fibrosis, renal scarring and dysfunction (33). Among the many cytokines involved in these processes, the vascular endothelial growth factor (VEGF) as well as the endothelial progenitor cells (EPC) seem to be the more relevant (35,36). From these experimental studies, several findings emerge that can be translated to patients with RAS. First is that the kidney contralateral to the stenotic one is affected by the similar humoral changes, supporting the notion that the ischaemic kidney is the source of factors that can have detrimental effects on the systemic circulation. This interpretation is in agreement with the observations that reversal of experimental RVH restores coronary microvascular function and architecture (37) and that for the same level of BP, the alterations of the microcirculation in patients with RVH are more severe than in those with essential hypertension (38). Second, after restoration of renal blood flow, the regression of hypoxia-induced changes in renal microvessels is only partial, delayed and not dependent on BP. This finding goes along with the observation that in patients with ARAS the recovery of GFR in the dilated kidney takes place progressively (39). Nowadays, renal tissue oxygenation is measurable with blood-oxygen level-dependent (BOLD) MR

imaging (40) and results of studies carried out in patients with ARAS before and after revascularization using this technique confirm the relationship between the degree of renal hypoxia and the markers of inflammation released from the stenotic and contralateral kidney (41).

## CLINICAL ASPECTS

Atherosclerotic RAS and renal FMD differ with respect to patient characteristics and prognosis. Severe or recent-onset hypertension, abdominal bruit, male gender, flash pulmonary oedema, hypercholesterolaemia, loss of renal function after treatment with an ACE inhibitor (ACEI) or an angiotensin receptor antagonist (ARA), a history of tobacco use and atherosclerosis elsewhere in the body are clinical clues which may arouse the suspicion of ARAS. This diagnosis may also be suspected in elderly patients, with hypertension and renal dysfunction as key symptoms. However, one should be cautious to reject ARAS in a patient who does not meet any of the above-mentioned criteria. Clinical prediction rules, such as the one proposed (42) and validated (43) by Krijnen et al., may assist the physician in the selection of patients who need to be investigated further, but even then, the chance of a positive result is not much greater than 30%. On the other hand, the odds of finding a lesion in the renal arteries markedly increases in preselected patient groups (Table 61.1) and when several clinical signs coexist. For instance, the combination of age above 60 years, diastolic BP greater than 110 mmHg and a serum potassium <3.3 mEq/L is associated with a nine-fold increase in the likelihood of finding an ARAS (44). Regardless of whether ARAS is found accidentally or after a deliberate search, or whether it is associated with hypertension or not, the long-term prognosis of patients with this abnormality is not very favourable (6,21,45), although this may be related to a concurrent decline in renal function more than to the RAS per se (46). Although renal impairment is frequently seen in patients with ARAS, progression to renal atrophy and renal failure occurs in 'only' about 20% of cases (47) but it doubles when ARAS is more than 75% at the time of diagnosis (48).

FMD is still considered to be a disease that affects mainly young women, although this paradigm is subject to debate, especially since we encounter an increasing number of older and male patients with FMD (49). Surely, if one looks for FMD only in young females, the association becomes a self-fulfilling prophecy, which tends to deny that older women who are first diagnosed with hypertension at a later age may have had the disorder all of their lives. However, it is important to recall that there are remarkable clinical differences between patients with multifocal and unifocal FMD. Indeed, the latter form is relatively more frequent in men, is diagnosed much earlier (on average at 15–20 years before) and is associated with more severe hypertension that responds better to revascularization (16). Thus far, no clues have been identified that are sensitive and specific enough to alert the physician to the diagnosis of FMD, but an association that is increasingly being recognized as important is that between FMD and pre-eclampsia (50). FMD and smoking were also found to be associated, but the mechanisms underlying this relationship are unclear (51). As pointed out above, one may also suspect renal FMD to be present when FMD has been

found in another vascular territory, for instance in the carotids (52). As for ARAS, the combination of quite specific clinical signs (abdominal bruit, early onset of severe hypertension, renal asymmetry) are strongly suggestive of severe renal FMD, and in our opinion, worth investigating directly with intra-arterial angiography.

## WHOM TO SCREEN AND HOW?

To screen patients for RAS, one can perform either a functional or an anatomical (imaging) test. While the latter is supposed to identify a culprit lesion, the former should detect a disturbance in physiological functions such as renal blood flow or renin release. Unfortunately, so far no consensus has been reached on which test is preferable or in which sequence they should be applied. Although functional tests would be ideal from a theoretical point of view, they have proven to be of limited value in the workup of patients in whom renal artery stenosis is suspected (53). Several years ago, Radermacher and associates suggested that the intra-renal resistance index, measured by duplex ultrasonography, could fairly accurately predict the response to renal angioplasty or surgery (54) and thus provide information about the hemodynamic significance of a stenosis. At least in patients with unilateral ARAS, there is a close correlation between the resistance index and the translesional pressure gradient (55). Also, other velocimetric indexes like acceleration and acceleration time that are less influenced by such confounding factors as age, intraparenchymal artery distensibility and renal function accurately detect ARAS and FMD with greater than 50% luminal reduction and have the additional advantage of reflecting the technical success of revascularization procedures as well as the restenosis of the dilated vessel (56,57). However, even though ultrasound represents the best available noninvasive procedure, it has not gained widespread acceptance, perhaps because it requires specific operator skills.

Imaging techniques include CTA and MR angiography (MRA), both of which have reasonable sensitivity and specificity, although with the limitation of a modest reproducibility (49). An obvious advantage of MRA is that no contrast material is needed, but this technique tends to overestimate the degree of stenosis and may miss FMD. It is safe but occasionally a patient turns out to be allergic to gadolinium. By and large, CTA seems to be a bit more reliable than MRA but adverse reactions to contrast material may be a problem, particularly in elderly or diabetic patients or those with proteinuric CKD (58). Moreover, CT-angiography better visualizes small calcifications, thereby providing a more accurate discrimination of FMD lesions versus atherosclerotic ones. Taken together, for the time being CTA probably is the best widely available screening test for RAS, although duplex ultrasound may be considered in specialized centres with extensive experience with this modality. A promising alternative to have a kind of 'in vivo' histology of artery lesions with an invasive investigation is to combine intravascular ultrasound with optical coherence tomography (OCT), a technique that provides high-resolution cross-sectional images and permits a comprehensive visualization of the inside of the vessel with evaluation of RAS severity and morphology (59).

Why is it that imaging techniques provide better overall results than functional tests? Although we are inclined to believe that the lack of accuracy of functional tests is

due to technical imperfections and/or poor quality of test characteristics, it may simply be that the pathophysiological concepts upon which the tests were based are wrong. For instance, renography with or without ACE inhibition has proven to be too unreliable for the diagnosis of (functional) renal artery stenosis even though the rationale of the test seems sound. Rather than dismissing the test as being inaccurate, we may have to conclude that the test result represents a mechanistic phenomenon that we do not yet fully understand.

Intra-arterial digital subtraction angiography remains the gold standard to confirm or exclude the diagnosis of RAS. In experienced centres, this procedure may be combined with determination of pressure gradients, intravascular ultrasound and/or renal vein renin sampling. Lateralization of renin may point towards a significant stenosis on the affected side and may predict a favourable response to dilation and/or stent placement. However, the number of exceptions is simply too high to make this a reliable test. In fact, the renal vein/renin ratio is more useful to detect patients with a totally occluded renal artery who will benefit from nephrectomy than for identifying patients in whom BP will fall after revascularization (60). Today, measurements of pressure gradients across the stenosis at baseline and during dopamine-induced hyperaemia (61,62) are being advocated more and more as the best method to ascertain whether a stenosis is hemodynamically significant or not, but evidence that this is the better tool is still lacking.

## TREATMENT

### REVASCULARIZATION

Treatment options include surgery (reconstructive or bench), percutaneous transluminal renal angioplasty (PTRA) with or without stenting and medical therapy. There has been only one prospective study which compared reconstructive surgery to angioplasty in patients with unilateral ARAS (63). Despite better patency of the renal arteries after surgery, the outcome in terms of BP and renal function after 2 years was similar. Together with the improvement in PTRA and stent procedures, this has led to a substantial decline in operative procedures for the treatment of atherosclerotic RAS. The question then is whether PTRA is any better than conventional (medical) treatment. Unfortunately, this issue has not yet been settled. Four major prospective randomized trials have evaluated the effect of PTRA with or without stenting on top of medical treatment as compared to that of medical treatment alone. These are DRASTIC (64), STAR (65), ASTRAL (66) and CORAL (7). At first glance, none of these trials showed any clear benefit of PTRA with or without stenting over and above the effect conferred by medical treatment. Of course, despite great technical achievements, it is still possible that in some cases after an angioplasty intervention, procedure-related factors (e.g. undetected dissection) help to sustain renal ischaemia rather than ameliorating it, but this would not be likely to explain the lack of effect in the whole trial.

On the other hand, the trials have been severely criticized for a variety of methodological limitations, of which sample size and patient selection are the most important (67,68). In 2016, an expert panel systematically reviewed all

data concerning the comparative effectiveness and safety of PTRAs plus stenting, surgical revascularization, and medical therapy to treat ARAS in regard to clinically important outcomes (69). The overall conclusion of this analysis was that the strength of the evidence is low so that there is no or only a minimal clinically important difference between these treatments with regard to outcome or BP control. In other words, we do not know whether mechanical treatment of the stenosis is good or bad. Van der Niepen and co-workers also reviewed the evidence and concluded that the trials fell short of including the right type of patients (70). They appropriately stated that the results of the trials argue against indiscriminately revascularizing all patients with ARAS. Nevertheless, there are probably subgroups of patients who would benefit more than others from such treatment (69–71). The same reasoning applies also to the possibility of rescuing renal function. While in patients with almost normal GFR, like those in the CORAL study (on average 58 mL/min), the expected benefits are small, in those with more advanced CKD (stage 4–5), the increase in GFR after restoration of renal blood flow may be substantial (72). In these patients, postponing revascularization to a later stage may abolish its beneficial effects because the ischaemia-induced intrarenal lesions have become irreversible. Moreover, the revascularization has the additional advantage of reducing the number of hospitalizations and improving heart failure control (73,74). For the time being, it is wise to select for angioplasty those patients with ARAS in whom hypertension is resistant to treatment or who respond to a lowering of BP with a decline in renal kidney function, whereas revascularization is mandatory in patients with bilateral ARAS and flash pulmonary oedema.

In patients with FMD, angioplasty is still the treatment of choice, although the effects are less clear-cut than once thought. As mentioned earlier, in a systematic analysis of 47 angioplasty studies and 23 surgery studies in FMD patients, Trinquart and co-workers concluded that the probability of being cured was approximately 30–50% and inversely associated with age (16). Renal angioplasty can be particularly rewarding in children in whom an adequate control of BP is very difficult despite the use of several antihypertensive drugs (75).

## MEDICAL TREATMENT

All patients with hypertension associated with RAS should be treated intensively with medical therapy. Unfortunately, there is no consensus on the optimal medical treatment. ACEIs, ARAs, calcium channel blockers and beta-blockers can all be used in the treatment of these patients. However, in several studies the antagonists of the RAS were found to be superior to other classes of antihypertensive agents, achieving BP goals in more than 80% of cases (47). Moreover, in observational studies treatment with ACE inhibitors was associated with increased survival during several years of follow-up (76). The drawback of ACEIs and ARAs is that reducing angiotensin II formation or antagonizing its action prevents the most relevant compensatory mechanism that maintains glomerular filtration pressure in poststenotic kidneys. Thus, in patients with unilateral RAS, treatment with ACEIs and ARBs may occasionally lead to substantial decrements in single kidney function. When serum creatinine is measured, this loss of function may be underestimated because of the compensatory increase

in GFR in the contralateral kidney. In any case, treatment with these drugs should be closely monitored, particularly in the early phases, with serum creatinine and potassium measurements, and treatment should be suspended whenever there is an increase in creatinine >20% above baseline values (77). The majority of these deteriorations in renal function are seen in patients with RAS in a single functioning kidney or in those with bilateral RAS, and represent a strong indication to attempt revascularization.

There are several good reasons to use beta-adrenergic-blocking compounds alone or in combination with ACEIs and ARAs to treat patients with RVH. One is that sympathetic overactivity is recognized in hypertensive patients with ARAS (78). In addition, beta-blockers suppress the neurally mediated component of renin release and, at variance with ACEIs and ARAs, have neutral effects on renal function (79). A recent retrospective study has shown that beta-blockers reduce mortality in patients with renovascular disease (80) as they do in the general CKD population (81). Calcium channel blockers are advantageous because of their vascular protective properties, but their use is limited by side effects and in the setting of incipient or overt heart failure. Diuretics are contraindicated in RVH because they can exacerbate the hyperactivity of the RAS. However, loop diuretics may be needed in patients with bilateral RAS or in the late, volume-dependent stages of RVH and when kidney function is markedly deteriorated. Aldosterone antagonists are very effective in resistant hypertension but must be used with caution if patients are already on treatment with ACEIs or ARAs because of the risk of inducing a further fall in GFR and dangerous hyperkalaemia. Preliminary evidence from uncontrolled studies suggests that also statins and antiplatelet drugs may have beneficial effects in patients with ARAS (82,83).

## CONCLUSIONS

After decades of intensive and painstaking research, the relationship between RAS and hypertension remains elusive. There are no clinical signs, biomarkers or imaging investigations to establish with certainty that RAS is the cause of high BP. In young patients, and particularly in many of those with unifocal FMD, the role of RAS is evident, considering the high rate of hypertension cure seen after revascularization. In most middle-aged or elderly patients ARAS seems to be superimposed on essential hypertension and aggravates an already extensive atherosclerotic burden rather than being the aetiology of BP elevation. Thus, not unexpectedly, in the majority of these patients the restoration of renal blood flow results, at best, in some improvement of BP control, whereas the outcome may be somewhat better in rescuing renal function in patients with advanced renal insufficiency. Notwithstanding the importance of the recent large randomized clinical trials that addressed the value of renal angioplasty versus medical treatment, the decision of whether to proceed to revascularization in individual patients with RAS cannot be taken according to their results with the logic 'one treatment fits all'. Rather, this decision rests on the responsibility of the clinician in charge and should be based on a number of factors that include age, type and severity of RAS, comorbidities, overall cardiovascular risk profile, efficacy of and adherence to medical therapy and, by no means equally important, expectations and wishes of the patient.



## REFERENCES

- Goldblatt H, Lynch J, Hanzal RF, Summerville WW. Studies on experimental hypertension: I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. *J Exp Med* 1934; 59(3): 347–379.
- Tigerstedt R, Bergman PG. Niere und Kreislauf. *Skand Arch Physiol* 1898; 8: 223–271.
- Robertson JIS. Renin and the pathophysiology of renovascular hypertension. In: Robertson JIS, Nicholls MG (eds) *The Renin-Angiotensin System*. 2. Gower Medical Publishing, London; 1993: 55.1–55.34.
- Lorenz EC, Vrtiska TJ, Lieske JC et al. Prevalence of renal artery and kidney abnormalities by computed tomography among healthy adults. *Clin J Am Soc Nephrol* 2010; 5(3): 431–438.
- de Mast Q, Beutler JJ. The prevalence of atherosclerotic renal artery stenosis in risk groups: A systematic literature review. *J Hypertens* 2009; 27(7): 1333–1340.
- Kalra PA, Guo H, Kausz AT et al. Atherosclerotic renovascular disease in United States patients aged 67 years or older: Risk factors, revascularization, and prognosis. *Kidney Int* 2005; 68(1): 293–301.
- Cooper CJ, Murphy TP, Cutlip DE et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med* 2014; 370(1): 13–22.
- Hendricks NJ, Matsumoto AH, Angle JF et al. Is fibromuscular dysplasia underdiagnosed? A comparison of the prevalence of FMD seen in CORAL trial participants versus a single institution population of renal donor candidates. *Vasc Med* 2014; 19(5): 363–367.
- Kadian-Dodov D, Gornik HL, Gu X et al. Dissection and aneurysm in patients with fibromuscular dysplasia: Findings from the U.S. Registry for FMD. *J Am Coll Cardiol* 2016; 68(2): 176–185.
- Olin JW, Gornik HL, Bacharach JM et al. Fibromuscular dysplasia: State of the science and critical unanswered questions: A scientific statement from the American Heart Association. *Circulation* 2014; 129(9): 1048–1078.
- Plouin PF, Baguet JP, Thony F et al. High prevalence of multiple arterial bed lesions in patients with fibromuscular dysplasia: The ARCADIA registry (Assessment of Renal and Cervical Artery Dysplasia). *Hypertension* 2017; 70(3): 652–658.
- Dorros G, Jaff M, Mathiak L et al. Four-year follow-up of Palmaz-Schatz stent revascularization as treatment for atherosclerotic renal artery stenosis. *Circulation* 1998; 98(7): 642–647.
- Ramsay LE, Waller PC. Blood pressure response to percutaneous transluminal angioplasty for renovascular hypertension: An overview of published series. *BMJ* 1990; 300(6724): 569–572.
- Rees CR. Stents for atherosclerotic renovascular disease. *J Vasc Interv Radiol* 1999; 10(6): 689–705.
- Iwashima Y, Fukuda T, Horio T et al. Association between renal function and outcomes after percutaneous transluminal renal angioplasty in hypertensive patients with renal artery stenosis. *J Hypertens* 2018; 36(1): 126–135.
- Trinquant L, Mounier-Vehier C, Sapoval M et al. Efficacy of revascularization for renal artery stenosis caused by fibromuscular dysplasia: A systematic review and meta-analysis. *Hypertension* 2010; 56(3): 525–532.
- Schwartz CJ, White TA. Stenosis of renal artery: An unselected necropsy study. *Br Med J* 1964; 2(5422): 1415–1421.
- Holley KE, Hunt JC, Brown Jr AL et al. Renal artery stenosis. A clinical-pathologic study in normotensive and hypertensive patients. *Am J Med* 1964; 37: 14–22.
- Hansen KJ, Edwards MS, Craven TE et al. Prevalence of renovascular disease in the elderly: A population-based study. *J Vasc Surg* 2002; 36(3): 443–451.
- Dustan HP, Humphries AW, Dewolfe VG, Page IH. Normal arterial pressure in patients with renal arterial stenosis. *JAMA* 1964; 187: 1028–1029.
- Mui KW, Sleeswijk M, van den Hout H et al. Incidental renal artery stenosis is an independent predictor of mortality in patients with peripheral vascular disease. *J Am Soc Nephrol* 2006; 17(7): 2069–2074.
- Wright JR, Shurrab AE, Cooper A et al. Left ventricular morphology and function in patients with atherosclerotic renovascular disease. *J Am Soc Nephrol* 2005; 16(9): 2746–2753.
- Rossi GP, Rossi A, Zanin L et al. Excess prevalence of extra-cranial carotid artery lesions in renovascular hypertension. *Am J Hypertens* 1992; 5(1): 8–15.
- Fava C, Minuz P, Patrignani P, Morganti A. Renal artery stenosis and accelerated atherosclerosis: Which comes first? *J Hypertens* 2006; 24(9): 1687–1696.
- Haimovici H, Zinicola N. Experimental renal-artery stenosis diagnostic significance of arterial hemodynamics. *J Cardiovasc Surg* 1962; 3: 259–262.
- Anderson WP, Johnston CI, Korner PI. Acute renal haemodynamic and renin-angiotensin system responses to graded renal artery stenosis in the dog. *J Physiol* 1979; 287: 231–245.
- Anderson WP, Korner PI, Johnston CI. Acute angiotensin II-mediated restoration of distal renal artery pressure in renal artery stenosis and its relationship to the development of sustained one-kidney hypertension in conscious dogs. *Hypertension* 1979; 1(3): 292–298.
- Caps MT, Perissinotto C, Zierler RE et al. Prospective study of atherosclerotic disease progression in the renal artery. *Circulation* 1998; 98(25): 2866–2872.
- Goncharenko V, Gerlock Jr AJ, Shaff MI, Hollifield JW. Progression of renal artery fibromuscular dysplasia in 42 patients as seen on angiography. *Radiology* 1981; 139(1): 45–51.
- van Twist DJ, Houben AJ, de Haan MW et al. Renal hemodynamics and renin-angiotensin system activity in humans with multifocal renal artery fibromuscular dysplasia. *J Hypertens* 2016; 34(6): 1160–1169.
- van Twist DJ, Houben AJ, de Haan MW et al. Pathophysiological differences between multifocal fibromuscular dysplasia and atherosclerotic renal artery stenosis. *J Hypertens* 2017; 35(4): 845–852.
- Bruyne B D, Manoharan G, Pijls NH et al. Assessment of renal artery stenosis severity by pressure gradient measurements. *J Am Coll Cardiol* 2006; 48(9): 1851–1855.
- Lerman LO, Textor SC. Gained in translation: Protective paradigms for the poststenotic kidney. *Hypertension* 2015; 65(5): 976–982.
- Gloviczki ML, Glockner JF, Lerman LO et al. Preserved oxygenation despite reduced blood flow in poststenotic kidneys in human atherosclerotic renal artery stenosis. *Hypertension* 2010; 55(4): 961–966.
- Chade AR, Kelsen S. Renal microvascular disease determines the responses to revascularization in experimental renovascular disease. *Circ Cardiovasc Interv* 2010; 3(4): 376–383.
- Chade AR, Kelsen S. Reversal of renal dysfunction by targeted administration of VEGF into the stenotic kidney: A novel potential therapeutic approach. *Am J Physiol Renal Physiol* 2012; 302(10): F1342–F1350.
- Urbiet-Caceres VH, Zhu XY, Gibson ME et al. Reversal of experimental renovascular hypertension restores coronary microvascular function and architecture. *Am J Hypertens* 2011; 24(4): 458–465.
- Rizzoni D, Muiesan ML, Porteri E et al. Relations between cardiac and vascular structure in patients with primary and secondary hypertension. *J Am Coll Cardiol* 1998; 32(4): 985–992.
- Airolidi F, Palatresi S, Marana I et al. Angioplasty of atherosclerotic and fibromuscular renal artery stenosis: Time course and predicting factors of the effects on renal function. *Am J Hypertens* 2000; 13(11): 1210–1217.
- Gloviczki ML, Glockner JF, Crane JA et al. Blood oxygen level-dependent magnetic resonance imaging identifies cortical hypoxia in severe renovascular disease. *Hypertension* 2011; 58(6): 1066–1072.
- Herrmann SM, Saad A, Eirin A et al. Differences in GFR and tissue oxygenation, and interactions between stenotic and contralateral kidneys in unilateral atherosclerotic renovascular disease. *Clin J Am Soc Nephrol* 2016; 11(3): 458–469.
- Krijnen P, Van Jaarsveld BC, Steyerberg EW et al. A clinical prediction rule for renal artery stenosis. *Ann Intern Med* 1998; 129: 705–711.
- Krijnen P, Steyerberg EW, Postma CT et al. Validation of a prediction rule for renal artery stenosis. *J Hypertens* 2005; 23(8): 1583–1588.
- Anderson GH, Jr., Blakeman N, Streeten DH. Prediction of renovascular hypertension. Comparison of clinical diagnostic indices. *Am J Hypertens* 1988; 1(3 Pt 1): 301–304.
- Amighi J, Schlager O, Haumer M et al. Renal artery stenosis predicts adverse cardiovascular and renal outcome in patients with peripheral artery disease. *Eur J Clin Invest* 2009; 39(9): 784–792.
- Aboyans V, Desormais I, Magne J et al. Renal artery stenosis in patients with peripheral artery disease: Prevalence, risk factors and long-term prognosis. *Eur J Vasc Endovasc Surg* 2017; 53(3): 380–385.
- Safian RD, Textor SC. Renal-artery stenosis. *N Engl J Med* 2001; 344(6): 431–442.

48. Tollefson DF, Ernst CB. Natural history of atherosclerotic renal artery stenosis associated with aortic disease. *J Vasc Surg* 1991; 14(3): 327–331.
49. Vasbinder GB, Nelemans PJ, Kessels AG et al. Accuracy of computed tomographic angiography and magnetic resonance angiography for diagnosing renal artery stenosis. *Ann Intern Med* 2004; 141(9): 674–682, discussion 82.
50. Vance CJ, Taylor RN, Craven TE et al. Increased prevalence of pre-eclampsia among women undergoing procedural intervention for renal artery fibromuscular dysplasia. *Ann Vasc Surg* 2015; 29(6): 1105–1110.
51. Savard S, Azarine A, Jeunemaitre X et al. Association of smoking with phenotype at diagnosis and vascular interventions in patients with renal artery fibromuscular dysplasia. *Hypertension* 2013; 61(6): 1227–1232.
52. Persu A, Giavarini A, Touze E et al. European consensus on the diagnosis and management of fibromuscular dysplasia. *J Hypertens* 2014; 32(7): 1367–1378.
53. Vasbinder GBC, Nelemans PJ, Kessels AGH et al. Diagnostic tests for renal artery stenosis in patients suspected of having renovascular hypertension: A meta-analysis. *Ann Intern Med* 2001; 135(6): 401–411.
54. Radermacher J, Chavan A, Bleck J et al. Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. *N Engl J Med* 2001; 344(6): 410–417.
55. Noory E, Rastan A, Beschoner U et al. Duplex derived intrarenal resistance index correlates with invasive pressure gradient measurements in detecting relevant unilateral renal artery stenosis. *Vasa* 2016; 45(2): 175–180.
56. Burdick L, Airolidi F, Marana I et al. Superiority of acceleration and acceleration time over pulsatility and resistance indices as screening tests for renal artery stenosis. *J Hypertens* 1996; 14(10): 1229–1235.
57. Marana I, Airolidi F, Burdick L et al. Effects of balloon angioplasty and stent implantation on intrarenal echo-Doppler velocimetric indices. *Kidney Int* 1998; 53(6): 1795–1800.
58. Rudnick MR, Goldfarb S, Wexler L et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: A randomized trial. The Iohexol Cooperative Study. *Kidney Int* 1995; 47(1): 254–261.
59. Athanasiou L, Sakellarios AI, Bourantas CV et al. Currently available methodologies for the processing of intravascular ultrasound and optical coherence tomography images. *Expert Rev Cardiovasc Ther* 2014; 12(7): 885–900.
60. Rossi GP, Cesari M, Chiesura-Corona M et al. Renal vein renin measurements accurately identify renovascular hypertension caused by total occlusion of the renal artery. *J Hypertens* 2002; 20: 975–984.
61. Leesar MA, Varma J, Shapira A et al. Prediction of hypertension improvement after stenting of renal artery stenosis: Comparative accuracy of translesional pressure gradients, intravascular ultrasound, and angiography. *J Am Coll Cardiol* 2009; 53(25): 2363–2371.
62. Mangiacapra F, Trana C, Sarno G et al. Translesional pressure gradients to predict blood pressure response after renal artery stenting in patients with renovascular hypertension. *Circ Cardiovasc Interv* 2010; 3(6): 537–542.
63. Weibull H, Bergqvist D, Bergentz SE et al. Percutaneous transluminal renal angioplasty versus surgical reconstruction of atherosclerotic renal artery stenosis: A prospective randomized study. *J Vasc Surg* 1993; 18(5): 841–850, discussion 50–2.
64. Jaarsveld BC V, Krijnen P, Pieterman H et al. The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. Dutch Renal Artery Stenosis Intervention Cooperative Study Group. *N Engl J Med* 2000; 342(14): 1007–1014.
65. Bax L, Woittiez AJ, Kouwenberg HJ et al. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: A randomized trial. *Ann Intern Med* 2009; 150(12): 840–848, W150-1.
66. Wheatley K, Ives N, Gray R et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med* 2009; 361(20): 1953–1962.
67. Noory E, Sritharan K, Zeller T. To stent or not to stent? Update on revascularization for atherosclerotic renovascular disease. *Curr Hypertens Rep* 2016; 18(6): 45.
68. Textor SC, Lerman LO. Paradigm shifts in atherosclerotic renovascular disease: Where are we now? *J Am Soc Nephrol* 2015; 26(9): 2074–80.
69. Balk EM, Raman G, Adam GP et al. *Renal Artery Stenosis Management Strategies: An Updated Comparative Effectiveness Review. Comparative Effectiveness Review No 179 (Prepared by the Brown Evidence-based Practice Center under Contract No 290-2015-00002-1).* Agency for Healthcare and Quality, Rockville, MD; 2016.
70. Van der Niepen P, Rossignol P, Lengele JP et al. Renal artery stenosis in patients with resistant hypertension: Stent it or not? *Curr Hypertens Rep* 2017; 19(1): 5.
71. Garovic VD, Textor SC. Renovascular hypertension and ischemic nephropathy. *Circulation* 2005; 112(9): 1362–74.
72. Kalra PA, Chrysochou C, Green D et al. The benefit of renal artery stenting in patients with atheromatous renovascular disease and advanced chronic kidney disease. *Catheter Cardiovasc Interv* 2010; 75(1): 1–10.
73. Gray BH, Olin JW, Childs MB et al. Clinical benefit of renal artery angioplasty with stenting for the control of recurrent and refractory congestive heart failure. *Vasc Med* 2002; 7(4): 275–279.
74. Kane GC, Xu N, Mistrik E et al. Renal artery revascularization improves heart failure control in patients with atherosclerotic renal artery stenosis. *Nephrol Dial Transplant* 2010; 25(3): 813–820.
75. Shroff R, Roebuck DJ, Gordon I et al. Angioplasty for renovascular hypertension in children: 20-year experience. *Pediatrics* 2006; 118(1): 268–275.
76. Losito A, Errico R, Santirosi P et al. Long-term follow-up of atherosclerotic renovascular disease. Beneficial effect of ACE inhibition. *Nephrol Dial Transplant* 2005; 20(8): 1604–1609.
77. van de Ven PJ, Beutler JJ, Kaatee R et al. Angiotensin converting enzyme inhibitor-induced renal dysfunction in atherosclerotic renovascular disease. *Kidney Int* 1998; 53(4): 986–993.
78. Johansson M, Elam M, Rundqvist B et al. Increased sympathetic nerve activity in renovascular hypertension. *Circulation* 1999; 99(19): 2537–2542.
79. Bakris GL, Hart P, Ritz E. Beta blockers in the management of chronic kidney disease. *Kidney Int* 2006; 70(11): 1905–1913.
80. Ritchie J, Green D, Alderson HV et al. Associations of antiplatelet therapy and beta blockade with patient outcomes in atherosclerotic renovascular disease. *J Am Soc Hypertens* 2016; 10(2): 149–158, e3.
81. Badve SV, Roberts MA, Hawley CM et al. Effects of beta-adrenergic antagonists in patients with chronic kidney disease: A systematic review and meta-analysis. *J Am Coll Cardiol* 2011; 58(11): 1152–1161.
82. Hackam DG, Wu F, Li P et al. Statins and renovascular disease in the elderly: A population-based cohort study. *Eur Heart J* 2011; 32(5): 598–610.
83. Cooper CJ, Haller ST, Colyer W et al. Embolic protection and platelet inhibition during renal artery stenting. *Circulation* 2008; 117(21): 2752–2760.



Gian Paolo Rossi

## INTRODUCTION

Primary aldosteronism (PA), a common, albeit markedly underdiagnosed cause of curable arterial hypertension, is characterized by plasma levels of aldosterone that are inappropriate for the salt/volume/ and blood pressure status and concur with low measurable levels of plasma renin (1–3). In the presence of a high or normal sodium intake, hyperaldosteronism results in sodium and water retention and potassium loss, with ensuing hypertension, hypokalaemia and several detrimental consequences on the cardiovascular system (4–19) that ultimately cause a high rate of atrial fibrillation, ischaemic and haemorrhagic stroke, ‘flash’ pulmonary oedema and myocardial infarction (20,21). An early identification of PA followed by diagnosis of its subtypes is therefore of paramount importance to prevent such complications, particularly in those patients who are curable with surgery (Table 62.1) (20). In fact, when guided by adrenal vein sampling, adrenalectomy can cure hyperaldosteronism in close to 98% of the patients with PA, whereas if surgery is not curative a target drug treatment can avoid the harmful consequences of PA, including damage to target organs (such as the heart, arterial wall, and kidneys) and cardiovascular events. The purpose of this review is to provide updated information on the strategy for identifying patients with PA and for subtype differentiation of PA, and to highlight current treatment modalities.

## PREVALENCE OF PRIMARY ALDOSTERONISM

Because of the misconception that PA is ‘a needle in a haystack’ (22), PA is usually overlooked as a potential cause of arterial hypertension and therefore is considerably underdiagnosed. This underdiagnosis can explain why a useless debate on the prevalence of PA in hypertensive patients went on for decades (23), and why its prevalence has been severely underestimated in patients with hypertension.

In 2006, available studies showed that the prevalence of PA ranged from 1.4–32.0% (median 8.8%) (22), thus indicating that at that time the true prevalence of PA

was practically unknown. However, based of retrospective observational studies, many experts believed that PA could be far more prevalent than usually thought (24–26). This gap of knowledge was eventually filled in by the publication of the first large prospective survey designed to provide solid data on the prevalence of PA, the Primary Aldosteronism Prevalence in HYpertension (PAPY) Study, which exploited use of a thorough diagnostic workup to establish the presence of PA and also a rigorous set of criteria – the four corners criteria – to diagnose an aldosterone-producing adenoma (APA) (27). This study showed that among consecutive patients who were newly diagnosed with hypertension and were referred to hypertension centres, about 11.2% had PA. Even more importantly, 4.8% of the patients had a surgically curable subtype of PA, which led the investigators to conclude that PA is the most common curable endocrine form of hypertension in referred patients with hypertension. Notably, more than half of the patients with an APA and 82% of those with a bilateral form of PA were found to be normokalaemic at presentation, indicating that idea that hypokalaemia is a *conditio sine qua non* for diagnosing PA is clearly wrong. Notwithstanding this and despite the fact that normokalaemic PA mimicking essential hypertension was described by Jerome Conn as early as 1965 (28), even today most doctors only search for PA if their patients with hypertension are hypokalaemic. Accordingly, many patients who might have PA but do not show hypokalaemia are never screened for PA with the investigations that are necessary to detect the disease. This was recently shown by a survey of Italian and German general practitioners, which reported that overall no more than 2% of their hypertensive patients are ever screened for PA, which explains why these family doctors reported a prevalence of the disease between 1–2% (29). This data collides strikingly with the more than threefold higher prevalence of PA found in general practice (30) and provides compelling evidence for the need of broader screening strategies (31).

The demonstration of cases of normoaldosteronaemic PA, in which the only clues to the disease is low plasma renin, which can coexist with severe drug-resistant hypertension and low serum K<sup>+</sup>, strongly suggests that many cases currently dismissed as low-renin primary (essential)

**Table 62.1** Forms of primary aldosteronism*Surgically not curable*

- Bilateral adrenal hyperplasia
- Unilateral aldosterone-producing adenoma with bilateral adrenal hyperplasia
- Familial hyperaldosteronism type I (also known as glucocorticoid-remediable aldosteronism)
- Familial hyperaldosteronism types III and IV

*Surgically curable*

- Aldosterone-producing adenoma (aldosteronoma)
  - Unilateral
  - Bilateral
- Primary unilateral adrenal hyperplasia
- Multinodular unilateral adrenocortical hyperplasia
- Ovary aldosterone-secreting tumour
- Familial type II hyperaldosteronism
- Aldosterone-producing adenoma or bilateral adrenal hyperplasia with concomitant pheochromocytoma
- Aldosterone-producing carcinoma

**Table 62.2** Patients who should be screened because of increased prior probability of primary aldosteronism<sup>a</sup>

- Sustained BP > 150/100 mmHg on each of three measurements obtained on different days
- Hypertension (BP > 140/90 mmHg) resistant to three conventional antihypertensive drugs (including a diuretic)
- Controlled BP (<140/90 mmHg) on ≥4 antihypertensive drugs
- Hypertension and spontaneous or diuretic-induced hypokalaemia
- Hypertension and adrenal incidentaloma
- Hypertension and sleep apnoea
- Hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years)
- Hypertension and first-degree relatives with PA

<sup>a</sup> According to the Endocrine Society Practice guidelines.

hypertension can in fact be unrecognized PA (32), as proposed by Dr Conn several decades ago (28).

There are profound consequences of the high prevalence of PA, documented in the PAPY Study (27) and confirmed in multiple surveys of selected cohorts (33–37) and in studies carried out in the general population by general practitioners (38,39), on the strategy to be exploited in the investigation of patients with hypertension. This is because knowledge of the prevalence of the disease in the population at risk is fundamental, along with the patient's clinical history, for estimating the prior (pre-test) probability that an individual hypertensive patient has of being affected by PA. The incremental gain is, in fact, maximized when the patient's pre-test probability of the disease is between 10–30% (40). This means that use of diagnostic tests for the screening of PA is justified if one can enrich the PA prevalence by selecting the categories of patients to be screened (Table 62.2) (27), therefore making the screening cost effective, a strategy endorsed by the current guidelines (41), as discussed in the next section.

## SCREENING STRATEGY

The Endocrine Society guidelines based their suggested strategy on the aforementioned cost-effectiveness

considerations since their first release (42); however, compared to their previous edition, the latest PA practice guidelines have widened the categories of patients that should be screened (41). Even though the general concept remains that the screening tests should be performed only in patients with a pre-test probability of PA higher than 10% (Figure 62.1 and Table 62.2), a wider screening strategy, such as testing for PA all newly presenting patients with hypertension, can be justified according to other experts (31). Use of this broader screening strategy is supported not only by the aforementioned data on the high prevalence of PA (43) but also by recent data supporting a natural history of PA, which starts with renin suppression and normotension, evolves into florid PA, and ultimately into stage II–III and/or drug-resistant hypertension (43,44). The recently evidenced possibility of preventing cardiovascular complications with an early diagnosis followed by specific treatment (21,45) also supports implementation of such broader screening strategies. Nonetheless, the latter can be too challenging on the healthcare systems of many countries, and furthermore, the bottleneck of the diagnostic workup involves the subtyping for establishing surgical curability by AVS, which is undoubtedly a challenging and not widely available test, as discussed later. As an accurate diagnosis opens the way to target treatment even when the indication for adrenalectomy cannot be posed, there is little doubt that the screening for PA is mandatory in the categories of patients listed in Table 62.2, particularly if the patients wish to accomplish long-term cure, are reasonable candidates for adrenalectomy, and/or have severe or drug-resistant hypertension. The latter categories comprise patients who usually present with unambiguous evidence of damage to their target organs and therefore are at a high risk of PA complications (46).

The demonstration of an inappropriate secretion of aldosterone that is autonomous from the renin–angiotensin system is the first step for diagnosing PA. On the basis on this premise, the aldosterone:renin ratio (ARR) has been introduced as a simplified approach for the detection of PA (47). However, it should be acknowledged that the ARR is a crude bivariate approach to the diagnosis, and that its use requires consideration of multiple issues (Table 62.3). For example, its value depends on plasma aldosterone concentration (PAC) and renin levels, implying that very different PAC and renin values can produce the same value of the ratio. Thus, a suppressed renin value will increase the ARR even when PAC is normal; moreover, all methods currently available for measuring plasma renin, including the plasma renin activity (PRA) assay, and also the newer direct active renin concentration (DRC) assay (48), lose their precision when levels of renin are low. Because of this, to avoid overinflating the ARR when levels of renin are very low, it is advised to fix at a minimum (which is 0.2 ng/mL/h for PRA and 2 mIU/L for DRC) the lowest renin value to be included in the calculation of the ratio. This precaution is crucial in some subgroups of patients who have low PRA values, such as the elderly and people of African origin (24). Thus, rather than using the ARR in a purely arithmetical way, the combination of an increased ARR and a PAC >12–15 ng/dL should be regarded as indicative of PA and used to detect this condition in patients.

I would, however, prefer using multivariate discriminant analysis strategies to achieve an accurate identification of PA, not only because they consider multiple variables at the same time besides PAC and renin, rather than just the ratio

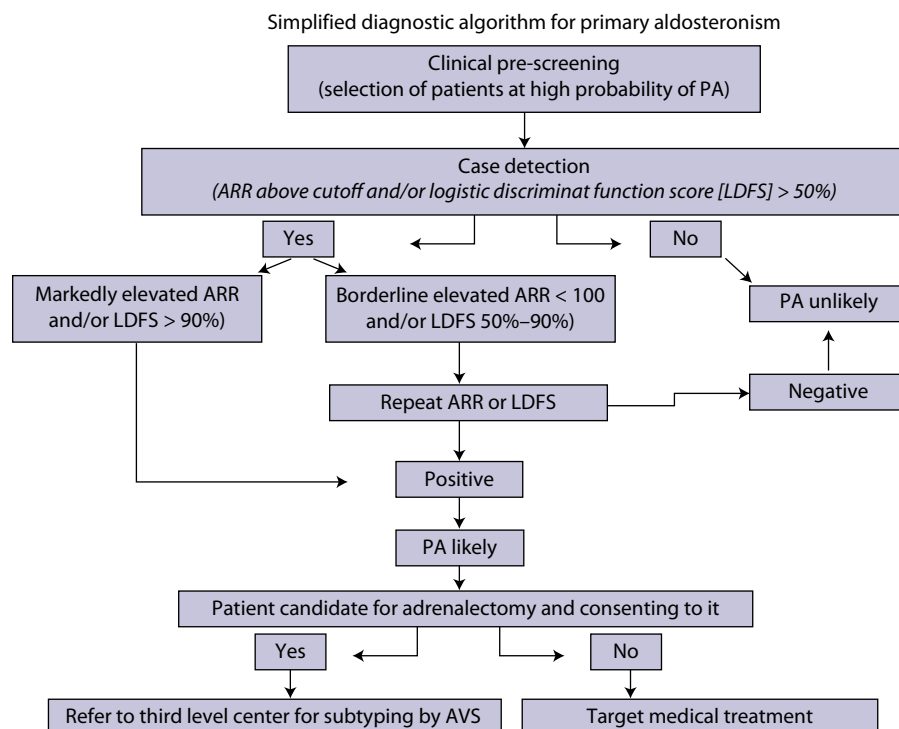


**Figure 62.1** Diagnostic workup of primary aldosteronism. The clinical pre-screening should allow identification of patients with a high pre-test probability of primary aldosteronism in whom to perform the screening tests. The latter should be highly sensitive in order not to miss cases; thus they carry a high false positive rate. The most used such screening test is the ARR, which carries important quantitative information. In patients with a high ARR (for example, higher than 100 when measured from PAC [ng/dL] and PRA [ng/m/h]) and/or a LDFS >90%, we proceed directly to subtype differentiation by adrenal vein sampling (see text). In those with an ARR at baseline (for example between 26 and 100 when measured from PAC [ng/dL] and PRA [ng/m/h]) and/or a LDFS between 50–90%, we repeat the screening tests under carefully standardized conditions and then proceed to subtyping if the ARR and/or the LDFS are confirmed to be raised. This approach is in line with that suggested in the Endocrine Society Practice Guidelines, which, however, recommend a confirmatory test in patients with equivocal ARR results. *Abbreviations:* ARR, aldosterone:renin ratio. LDFS, logistic discriminant function score; AVS, adrenal vein sampling.

of only the latter variables, but also because they make use of the absolute value of these variables (49,50). Therefore, these strategies have the additional advantage of providing an estimate of the individual patient's probability of developing PA, which enables the clinician to decide, based on this probability, whether to proceed with further testing. One such function has been published and can easily be implemented for use in commercially available worksheets and adapted for decision-making in clinical practice (50). It has also been implemented in an ARR app. In fact, one problem commonly encountered by physicians when dealing with the laboratory report of renin and aldosterone entails the different methods and units used in the different laboratories. To overcome these difficulties, we have created an application, the ARR app, which is described in detail elsewhere (51).

Notwithstanding its many limitations, the ARR still remains the most popular test because of its simplicity. Despite some pessimistic expectations, we found that when repeated under carefully standardized conditions it shows a considerable within-patient reproducibility (52). Moreover, it conveys quantitative information, which is commonly neglected when the ratio is interpreted in a purely categorical way, e.g. as positive or negative. In other

words, if the ARR value (determined under standardized conditions) is noticeably raised, a biochemical diagnosis of PA can be made and there is no need for further testing. Therefore, one can proceed directly to referring the patient for subtyping following a simplified diagnostic algorithm (Figure 62.1). This means a remarkable simplification of the workup, which saves a good deal of time and money for the management (53).

In the largest study, where the diagnosis of APA was used as the gold standard and the investigators used receiver operating characteristic (ROC) curves and the Youden index, the optimal cutoff which corresponded to a sensitivity of 80.5% and a specificity of 84.5% of the ARR (calculated from PAC and PRA in ng/dL/ng/mL/h) was 26 (27), with lower cutoff values increasing sensitivity at the expense of specificity. With use of an automated chemiluminescent assay that provides measurement of PAC and DRC at the same time, the corresponding cutoff was 2.06 (calculated from PAC in ng/dL and DRC in mUI/L), as ascertained in a prospective study of a large cohort of PA patients (48). With this cutoff, the sensitivity for the identification of APA was 92%, the specificity 91.6%, and the area under the ROC curve, an estimate of overall accuracy,

**Table 62.3** Suggestions for the correct use of the ARR as a screening test

| Factors affecting ARR               | Suggestion                                                                                                                                                                                                                                                                                          |
|-------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Serum levels of potassium           | Correct hypokalaemia, if present, before performing the test to avoid false negative ARR values                                                                                                                                                                                                     |
| PAC                                 | Be aware that high PAC might originate from low salt intake or use of diuretics<br>Prepare patient with adequate salt intake, measure 24-h urinary sodium excretion<br>Withdraw diuretics at least 3–4 weeks before testing; mineralocorticoid receptor antagonists at least 6 weeks before testing |
| Renin assay                         | Because of low precision of the PRA or DRC assay for low renin values, fix the lowest level of renin to be used in the ARR                                                                                                                                                                          |
| Patient position and blood sampling | Standardize the position of the patient and sampling conditions at your centre                                                                                                                                                                                                                      |
| Handling of the samples             | Be aware that handling and storage of plasma samples differ for PRA and DRC assays                                                                                                                                                                                                                  |
| Drugs                               | $\alpha_1$ -receptor blocker doxazosin and long-acting calcium channel blockers are allowed                                                                                                                                                                                                         |
| ARR accuracy                        | The cutoff value that provides the best combination of sensitivity and specificity should be identified at each centre by ROC curves<br>Be aware that the ARR is a crude bivariate analysis and that multivariate logistic discriminant analysis might provide better diagnostic accuracy           |

Abbreviations: ARR, aldosterone:renin ratio; PAC, plasma aldosterone concentration; PRA, plasma renin activity; DRC, direct active renin; ROC, receiver operating characteristic.

was 0.974 (95% CI: 0.940–0.991). Thus if the ARR is properly determined, a markedly raised value is a strong indication that the patient has PA.

Some important points must be made concerning the assay to be used for renin measurement. The DRC assay is becoming popular because of several advantages, including the fact that samples are handled at room temperature (48). However, freezing or exposing samples to low temperatures during this assay can artificially raise the value, owing to cryoactivation (54–56). By contrast, when using the PRA assay, handling plasma at room temperature can lead to angiotensin I generation angiotensinogen consumption and high blank values, which can result in underestimation of the levels of renin.

If the samples are properly collected for each assay, the DRC and PRA values show a good correlation (57), as we recently showed (48). This correlation is weak when the levels of renin are low and strong when renin is stimulated (58); however, in patients with PA the levels of renin are typically low (58), and therefore the DRC should be preferred. Besides the sample collection at room temperature,

the DRC chemiluminescent assay has several additional advantages over the PRA assay because it lends itself to automation and thus requires less manpower, and furthermore, implies lack of radioactive waste. For all these reasons, at my institution we have replaced the PRA with the PAC/DRC automated assay, and this replacement is rapidly occurring throughout the globe (48).

## CONDITIONS FOR TESTING

Careful preparation of the patient is a key step in screening for PA, as described in Table 62.3. The patients should be tested after they have been kept resting supine, or sitting quietly, for 1 hour. A concomitant 24-hour collection of urine to measure urinary sodium excretion provides an assessment of the electrolyte intake, which is crucial for a correct interpretation of the renin and aldosterone values. Likewise, measurement of the serum levels of potassium is helpful to exclude hypokalaemia that if present reduces aldosterone secretion and can lead to factitiously negative ARR results.

Because most antihypertensive drugs affect PAC, renin values or both, and thereby the ARR, treatment must be properly modified before measuring the levels of aldosterone and renin. A few agents have negligible effects on the ARR; for example, the  $\alpha_1$  receptor blockers doxazosin and terazosin have no effect on the renin–angiotensin–aldosterone system, while long-acting calcium channel blockers can only slightly reduce the secretion of aldosterone (27,54,55). Complete withdrawal of antihypertensive drugs is never necessary; therefore, these agents can be used alone or in combination to control blood pressure during screening (49,54,55). When the patient needs a treatment stronger than with only these agents, as in patients with severe and/or drug-resistant hypertension, with evidence of target-organ damage or previous cardiovascular events, some hints can assist in interpreting the ARR and making the correct diagnosis. For example, a high PAC ( $> 15$  ng/dl) in a patient on drugs that would be expected to lower aldosterone, and/or a reduced level of renin despite receiving agents that are expected to raise the level of renin, are strong indications that the patient could have PA, and therefore should be investigated further. A skilled clinician can therefore confirm or exclude the diagnosis of PA even in these challenging patients, by considering knowledge of the effects of the different drugs on the ARR and its components. An ongoing study is testing the feasibility of measuring the ARR in patients receiving a mineralocorticoid receptor antagonist (MRA), alone or in combination with an angiotensin type 1 receptor antagonist (59). The results of this study are long awaited since, if proven, this feasibility might allow to screen for PA also patients with drug-resistant hypertension, a common presentation of PA, that, according to the latest guidelines (60), should receive an MRA.

## EXCLUSION OF PRIMARY ALDOSTERONISM

To avoid missing any patients with PA, the screening tests are set to be highly sensitive (Figure 62.1). This implies that they often give false positive results that must be identified to the aim of excluding the patient from AVS.



The oral sodium loading test, the saline infusion test, the captopril challenge test and the fludrocortisone with salt loading test have been put forward as 'confirmatory' tests. In reality, what they actually serve for is to exclude false positive results, because at the prevalence rate commonly encountered at hypertension centres their negative predictive value (exclusion) value largely exceeds their positive predictive (confirmatory) value (56,57).

The general purpose of these tests is to demonstrate that the excess secretion of aldosterone is autonomous from the renin-angiotensin system, but unfortunately this premise is false inasmuch as in many patients with idiopathic hyperaldosteronism and also with APA, aldosterone secretion is dependent on angiotensin, as shown in the aforementioned PAPY study (Figure 62.2) (61). Relying on these tests can thus lead to missing several patients with curable APA, who show suppressible aldosterone excess after blunting the levels of renin (62–65). According to a recent very large study, the diagnostic gain provided by one such test, the captopril challenge, was negligible over an ARR performed in carefully standardized conditions (53). Thus, as mentioned earlier, once a markedly raised ARR, for example >100 (when using PAC in ng/dL and PRA in ng/mL/h), has been found, it is justified to proceed directly with AVS if the patient is willing to pursue a surgical cure (52), an approach shown in Figure 62.1 that is consistent with the suggestion of the latest Endocrine Society guidelines to skip the confirmatory tests in patients with a florid PA phenotype (41).

If one preferred to perform a 'confirmatory' test anyway, it has to be considered that at a low sodium intake the saline infusion test is more accurate than the captopril test, which should therefore be used only after increasing sodium intake to >6.3 g NaCl per day (65). Moreover, as mentioned earlier, both tests are more specific than sensitive at their optimal cutoff values in referred patients (Figure 62.3) (49,65). This feature means that these tests are more useful to exclude, rather than confirm, the

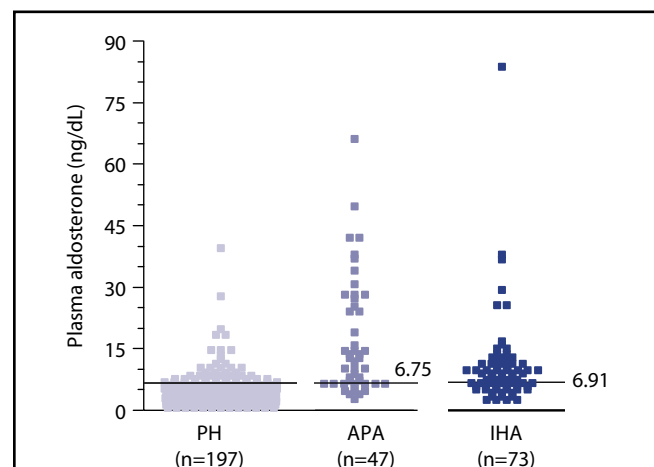


**Figure 62.2** The plot shows the PAC values after saline in the patients with primary (essential) hypertension (PH), APA (confirmed by the four corners criteria) and idiopathic aldosteronism (IHA) of the PAPY study. Please note the huge overlap of values both below and above the cut-off that makes this test unreliable in attributing patients to one group or another. (Reproduced with permission from Rossi GP et al. *J Hypertens* 2007; 25: 1433–1442.)

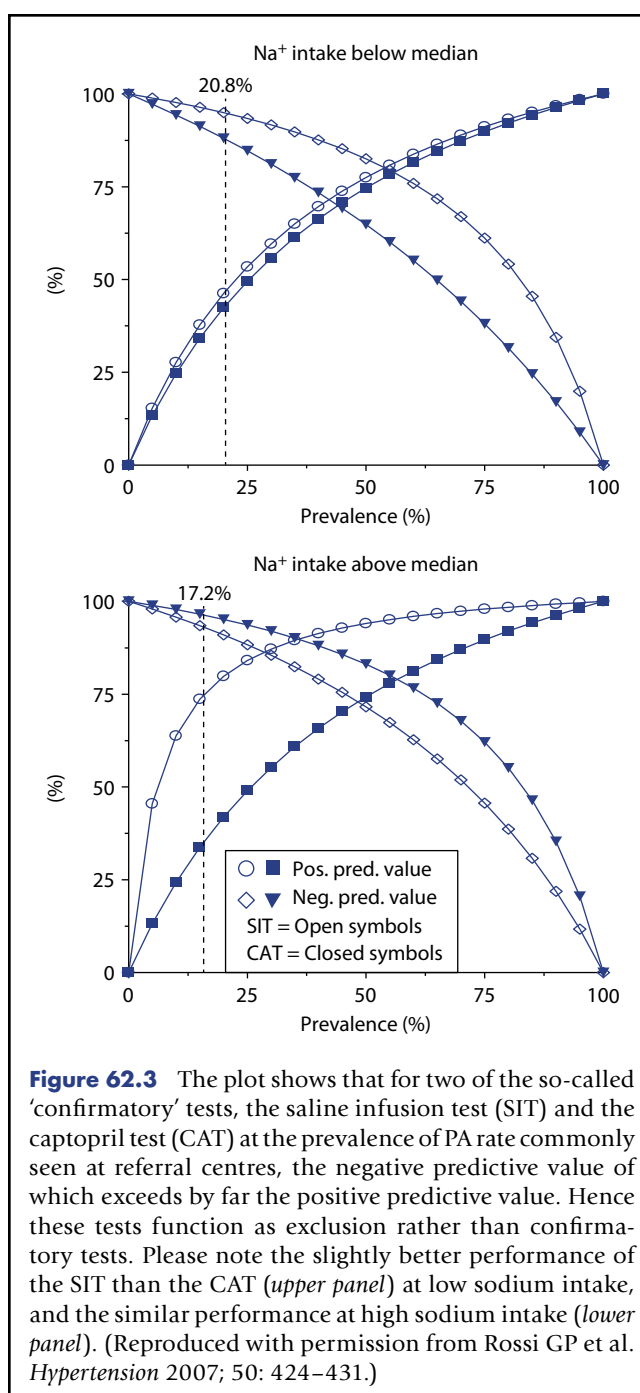


**Figure 62.3** The plot shows that for two of the so-called 'confirmatory' tests, the saline infusion test (SIT) and the captopril test (CAT) at the prevalence of PA rate commonly seen at referral centres, the negative predictive value of which exceeds by far the positive predictive value. Hence these tests function as exclusion rather than confirmatory tests. Please note the slightly better performance of the SIT than the CAT (upper panel) at low sodium intake, and the similar performance at high sodium intake (lower panel). (Reproduced with permission from Rossi GP et al. *Hypertension* 2007; 50: 424–431.)

presence of PA, and therefore they should be regarded as exclusion rather than as confirmatory tests (65). Finally, some experts contend that the fludrocortisone with salt loading test would be the most specific exclusion test (55) and should be a gold standard test, but this test has been abandoned at most centres because it requires a costly hospitalization for surveillance of the patient, owing to the risk of worsening hypertension and hypokalaemia.

Some clinicians prefer the measurement of urinary aldosterone because they hold it to provide an estimate of aldosterone production integrated over 24 hours. However, only 15–20% of the aldosterone excreted in urine is 18-glucuronide, which is the substance usually measured to assess the



excretion of aldosterone in the urine. In fact, aldosterone is mainly metabolized to tetra-hydro-aldosterone, which implies that if the laboratory does not take proper precautions to measure all forms of aldosterone, only a small fraction of aldosterone is being measured, particularly if the pH of urine is not kept close to 1. For these reasons, the measurement of urinary aldosterone does not furnish an accurate estimate of the true aldosterone secretion in all laboratories, which probably explains why in some centres urinary aldosterone was not found to discriminate between patients with and without PA as well as expected.

## IMAGING OF PRIMARY ALDOSTERONISM

According to guidelines, all PA patients should undergo an imaging test, preferably by CT, for two main reasons: (i) to exclude carcinoma, which are usually large and display Hounsfield units >15, and (ii) to identify adrenal venous drainage, thus offering some guide to the interventionist performing AVS (67,68). Compelling evidence, however, exists that imaging alone is insufficient to refer the patient to surgery: in 2004, a Mayo Clinic study examining the diagnostic accuracy of a CT-based strategy for the subtyping of PA, using cosyntropin-stimulated AVS as a reference test, found concordant results between tests in only 53.1% of the cases, unilateral disease at AVS in 22.2% CT-negative cases, and unilateral mass at CT with bilateral or contralateral disease at AVS in 24.7% of the cases (69). Relying on CT alone would therefore have led to denial of curative adrenalectomy to 22% of the patients and to unnecessary or inappropriate adrenalectomy in 24%. These findings led the authors to conclude that AVS is essential to distinguish between unilateral and bilateral PA. Common experience, anecdotal reports (8), and countless further studies support this conclusion. In 2009, Kempers et al. retrospectively analysed 38 studies comprising a total of 950 patients with the aim of determining the diagnostic accuracy of imaging for the subtyping of PA (70). A major limitation of this study was the lack of follow-up data in the articles that could be examined, which rendered it impossible to confirm that adrenalectomies were performed appropriately. Importantly, 38% of the patients showed discordant results between AVS and CT/MRI. If only CT/MRI had been used to determine lateralization, inappropriate adrenalectomy would have occurred in 15% of the patients where AVS showed a bilateral cause. Furthermore, inappropriate exclusion from adrenalectomy would have occurred in 19% where AVS showed unilateral secretion, and adrenalectomy on the wrong side would have occurred in 4%. The authors concluded that CT/MRI misdiagnosed the cause of PA in 38% of the patients, and that relying only on CT/MRI can lead to inappropriate treatment of many patients with PA.

A larger 19-year single-centre experience in patients who underwent unilateral adrenalectomy for the treatment of PA supports similar conclusions, with the caveat that long-term postoperative follow-up was obtained only in 54% of the 263 patients (71). In the patients submitted to adrenalectomy for presumptive unilateral disease, the overall effective cure rate of PA was 96%. In the biochemically cured PA patients, hypertension was cured in 42% and improved 46%; moreover, PA was not cured with unilateral adrenalectomy only in 4% of the patients. AVS was 97% accurate, while adrenal imaging was concordant to

the surgically documented side in 59%. Despite the overall poor accuracy of CT and MRI in detecting unilateral disease, adrenal imaging seemed to perform well in the patients younger than 35 years of age, but there were only six patients with these features (72).

A more recent German study reached similar conclusions concerning the poor performance of imaging. Despite AVS demonstration of lateralized disease, MRI and CT showed bilaterally normal adrenals in 17% and 9% of the cases, respectively (10). Unilateral enlargement of the non-hypersecreting adrenal gland was seen in 3% and 12% of the patients, respectively. In addition, bilateral pathology was seen in 17% and 22% of the patients with lateralized PA. Therefore, quite reasonably the authors concluded that: (i) the assessment of adrenal microadenomas is the main limitation of adrenal CT, (ii) both CT and MR imaging have a poor accuracy in predicting unilateral disease, and therefore (iii) AVS remains the essential diagnostic step to identify patients who may benefit given unilateral laparoscopic adrenalectomy.

## SUBTYPE DIFFERENTIATION BY AVS

Given the fallacies of the imaging tests, AVS remains the key technique for diagnosing unilateral production of aldosterone (41,68), but it is expensive, technically demanding, and carries a very small, but not negligible, risk of adrenal vein rupture (69,73). As an indication for adrenalectomy, AVS should only be used in patients with unequivocal biochemical evidence of PA in whom the surgically incurable forms of mineralocorticoid excess have been excluded (Figure 62.4) (74). Furthermore, patients selected to undergo AVS must be candidates for general anaesthesia and surgery, and must be willing to achieve long-term cure of PA with adrenalectomy.

The Endocrine Society guidelines state that AVS is the 'standard test to differentiate unilateral from bilateral causes of [PA]' (41). Accordingly, as we consider unethical undertaking of surgery without evidence of lateralized aldosterone secretion, at my institution we offer AVS to all patients before adrenalectomy. By contrast, some centres advocate a discriminating use of AVS and contend that this test might not be needed in patients <35 years old with solitary unilateral apparent adenoma on CT scan (75), based on the premise that the prevalence of non-functioning adenoma (incidentaloma) increases with age, and therefore an adrenal mass in a patient <35 years old with PA 'must be an APA'. The logical ground of this reasoning is, however, weak because the hyperaldosteronism and incidentaloma are independent conditions, which means that one does not exclude the other, and vice-versa. Moreover, the rarity of incidentaloma before age 40 years does not mean that an adrenal node in a patient with PA is automatically an APA, as PA can be attributable to micronodular bilateral adrenal hyperplasia or to a small APA that is invisible on CT scan and is contralateral to the identified node.

Moreover, familial hyperaldosteronism type I, II, III and IV, which cause bilateral adrenocortical hyperplasia due to germ-line mutations (76,77), are best treated medically as they are not surgically curable. Thus, whenever there is a family history of PA, use long PCR or sequencing to exclude the presence of such familial forms before offering AVS to the patients.

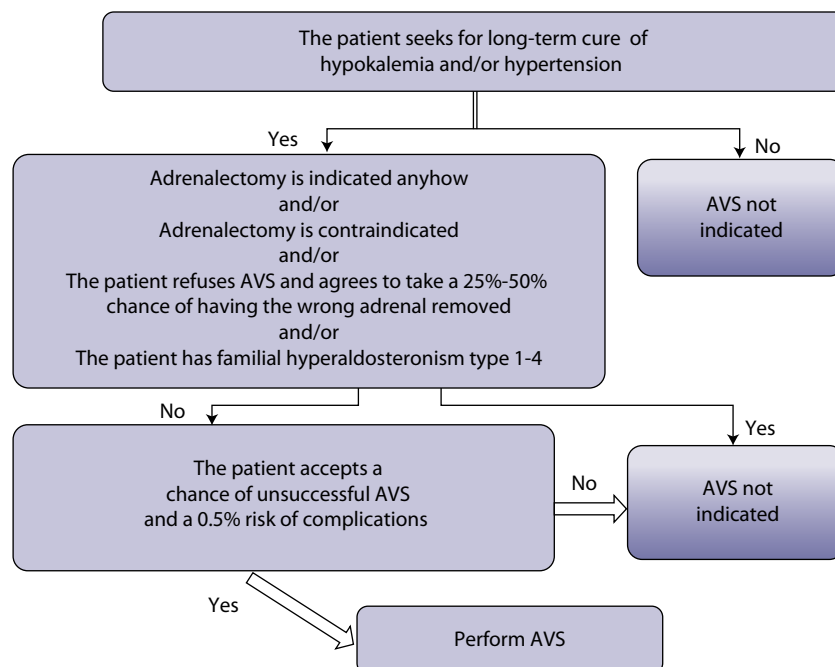


**Figure 62.4** Flow chart for selecting the patients with primary aldosteronism to be submitted to adrenal vein sampling.

As considerable experience is required for the performance and interpretation of AVS, this test should only be done in tertiary referral centres. An in-depth discussion of the issues surrounding the use of AVS is provided elsewhere (74,78), and only the key information is given herein to enable practicing physicians to prepare their patients for AVS and to select appropriate referral centres for their patients with PA.

First, to minimize the chance of false results, AVS should be undertaken after the withdrawal, if feasible, of all confounding drugs or after tapering treatment that reduces the levels of aldosterone as indicated for the screening test (Table 62.4). Second, hypokalaemia, if present, should be corrected, or after tapering treatment, before AVS, as hypokalaemia reduces aldosterone secretion and therefore can minimize lateralization, thus increasing the chances of false negative results. Third, use of bilaterally simultaneous catheterization during AVS (79,80) avoids generating artificial differences between the adrenal glands owing to the different timing of the blood sampling during AVS, which is a stressful situation (79). Bilaterally simultaneous catheterization is essential particularly when AVS is performed without adrenocorticotrophic hormone (ACTH) stimulation. Fourth, a major source of variation in the interpretation of AVS results is the difficulty of catheterizing the right adrenal vein, which is short and sometimes shares a common egress with inferior accessory hepatic veins. In the latter condition, mixing of adrenal blood with liver blood dilutes the plasma cortisol concentration (PCC) and PAC (81), and thus AVS can show levels of cortisol and aldosterone that are even lower than peripheral values owing to liver metabolism of the steroids. Superselective catheterization of the right adrenal vein after identification of the hepatic vein by CT (74,82), or after rapid measurement of cortisol levels in the adrenal vein during AVS (83,84), can circumvent this problem.

The measurement of PCC, besides that of PAC, in adrenal vein blood is used for calculation of the selectivity index (74), which helps in confirming catheter placement and correcting for dilution during sampling (85). This measurement is also crucial for calculating the lateralization index (78), for example, the PAC:PCC ratio on the dominant side over the PAC:PCC ratio on the contralateral side of the adrenal gland, which usually provides an accurate diagnosis (74).

Cosyntropin stimulation facilitates the ascertainment of selectivity but has a confounding effect on the lateralization index (86), which means that the value of aldosterone levels after ACTH stimulation can lead to the removal of the wrong adrenal gland. Therefore, this stimulation should be used only at centres with a low success rate in achieving selective cannulation (87). For a discussion of the pros and cons of using cosyntropin the readers are referred to a recent debate (88).

Assessment of the results of AVS as a lateralization index ignores a finding that is widely recognized but seldom reported and discussed. The secretion of hormones from the contralateral adrenal gland is rarely suppressed to levels similar to peripheral values and is most often higher than the peripheral values. Moreover, experimental studies have shown that aldosterone secretion persists even during prominent sodium loading and studies using in situ hybridization and immunohistochemistry have shown persistent aldosterone synthesis in the adrenal cortex surrounding an APA (89,90). Notwithstanding these limitations, some have proposed a contralateral suppression index (calculated as a PAC:PCC ratio in the contralateral [nondominant] adrenal gland lower than the PAC:PCC ratio in the peripheral vein or the infrarenal inferior vena cava) (91), but the accuracy of this index for the identification of unilateral causes of PA remains to be conclusively proven to data (74).

Hence, to address the several issues that remain controversial and/or unresolved in the interpretation of results

**Table 62.4** Effects of drugs and conditions

| Factor                                   | PAC | Renin           | ARR             | False positive rate | False negative rate |
|------------------------------------------|-----|-----------------|-----------------|---------------------|---------------------|
| <i>Medications</i>                       |     |                 |                 |                     |                     |
| $\beta$ -blockers                        | ↓   | ↓↓              | ↑               | ↑↑                  | ↓                   |
| Central $\alpha_2$ agonists              | ↓   | ↓↓              | ↑               | ↑                   | ↓                   |
| NSAIDs                                   | ↓   | ↓↓              | ↑               | ↑                   | ↓                   |
| K <sup>+</sup> -losing diuretics         | ↑   | ↑↑              | ↓               | ↓                   | ↑                   |
| K <sup>+</sup> -sparing diuretics        | ↑   | ↑↑              | ↓               | ↓                   | ↑                   |
| Angiotensin-converting enzyme inhibitors | ↓   | ↑↑              | ↓               | ↓                   | ↑                   |
| Angiotensin II receptor blockers         | ↓   | ↑↑              | ↓               | ↓                   | ↑↑                  |
| Long-acting calcium channel blockers     | →↓  | →               | ↓               | →↓                  | →↑                  |
| Renin inhibitors                         | ↓   | ↓↑ <sup>a</sup> | ↓↑ <sup>a</sup> | ↓↑ <sup>a</sup>     | ↓↑ <sup>a</sup>     |
| <i>Potassium status</i>                  |     |                 |                 |                     |                     |
| Hypokalaemia                             | ↓   | →↑              | ↓               | ↓                   | ↑                   |
| Potassium loading                        | ↑   | →↑              | ↑               | ↑                   | ↓                   |
| <i>Sodium status</i>                     |     |                 |                 |                     |                     |
| Sodium depletion                         | ↑   | ↑↑              | ↓               | ↓                   | ↑                   |
| Sodium loading                           | ↓   | ↓↓              | ↑               | ↑                   | ↓                   |
| Ageing                                   | ↓   | ↓↓              | ↑               | ↑                   |                     |
| <i>Other conditions</i>                  |     |                 |                 |                     |                     |
| Renal impairment                         | →   | ↓               | ↑               | ↑                   | ↓                   |
| Pregnancy                                | ↑   | ↑↑              | ↓               | ↓                   | ↓                   |
| Renovascular                             | ↑   | ↑↑              | ↓               | ↓                   | ↑                   |
| Malignant                                | ↑   | ↑↑              | ↓               | ↓                   | ↑                   |

Note:  $\beta$ -blockers reduce levels of renin but affect PAC relatively less, thus raising the ARR (47); therefore it is better to stop administering them at least 3–4 weeks before the assay, as failure to do so increases the false positive rate. Drugs that raise the PRA more than PAC, such as diuretics and mineralocorticoid receptor antagonists, should be withdrawn (at least 3–4 and 6 weeks before, respectively) to reduce the rate of false negative diagnoses. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and renin inhibitors raise renin and reduce aldosterone secretion. Therefore, they reduce the ARR and markedly increase the false negative rate. Because of this, they also should be withdrawn at least 3–4 weeks before performing the ARR.

<sup>a</sup> Renin inhibitors lower PRA but raise DRC. This effect would be expected to increase false positives when renin is measured as PRA, and false negatives for renin measured as DRC.

Abbreviations: ARR, aldosterone: renin ratio; DRC, direct active renin; PAC, plasma aldosterone concentration; PRA, plasma renin activity.

from AVS, the Adrenal Vein sampling International Study has gathered on >2500 AVS studies carried out at centres scattered across Europe, Asia and North America. This study has shown that AVS is being offered not to all but only to a variable proportion of PA patients, even though the rate of major complications is extremely low (0.57%), thus dispelling the idea that AVS is dangerous (91).

A challenge to the overwhelming evidence and the current guidelines recommendation to perform AVS in all patients with PA came by results of a recent prospective, randomized, controlled study of 184 patients, who received either an AVS-based or a CT-based treatment (92), which reported that after 1 year follow-up the intensity

of antihypertensive medication needed for obtaining the target blood pressure (in DDD), and the median (RAND-36) physical or mental scores did not differ significantly between the groups exposed to the two diagnostic strategies. This led the authors to conclude that the increased healthcare costs related to AVS were not justified by improvements in the quality of life, a claim that was not new, as similar statements were made before by at least two retrospective observational studies (93,94). Unfortunately, this trial has so many limitations that its conclusions are hardly acceptable. The most important of these limitations regards the selection of the patients, the choice of the primary endpoints, the suboptimal use of AVS and the total

lack of adequate statistical power, as recently discussed in depth (95). The primary endpoint (DDD 1 year post intervention) was a not a proper outcome measure inasmuch as AVS fattened by adrenalectomy is not recommended to lower the intensity of drug treatment necessary for obtaining target blood pressure, but rather to cure patients from PA. A worthier analysis would have compared biochemical resolution of PA, correction of hypokalaemia, and a rise in renin/fall in aldosterone into the normal range as primary endpoints, plus levels of complete remission of hypertension/partial remission/no change, or increase, as clinical endpoints. Notably, in the AVS and the CT group, persistent PA at 1-year follow-up, was found in 11% and 20% of the adrenalectomized patients, respectively, which is in striking contrast with the biochemical cure rate between 96–100% seen in larger AVS-based studies even by exploiting a much longer follow-up (21) and in a large retrospective international survey (96). As regards power, the authors calculated the sample size needed to achieve 80% power to detect a difference in DDD between groups, assuming a 1.8 SD, was 81 patients per arm for a two-sided  $\alpha = 0.05$ . Because their patients went into subgroups of 46 (in medical and surgical arms), only 46 patients underwent adrenalectomy in both arms. With this smaller sample size, the power of the study was reduced to ~50%, e.g. equivalent to tossing a coin. The authors' interpretation of those findings that 'Treatment of primary aldosteronism based on CT or AVS did not show significant differences in intensity of antihypertensive medication or clinical benefits for patients after 1 year of follow-up ... challenges the current recommendation to perform AVS in all patients with primary aldosteronism' (18) is a straightforward example of reverse 'spin' (97), e.g. to report that one approach was not beneficial while in fact it is (95). The superiority of AVS-guided adrenalectomy over CT in terms of biochemical outcome, albeit not of clinical outcome in a recent retrospective multi-centre survey (98), and also of clinical outcome has also been found in the largest registry of patients submitted to AVS worldwide (99).

### **<sup>11</sup>C METHOMIDATE POSITRON EMISSION TOMOGRAPHY**

<sup>11</sup>Cmethomidate positron emission tomography seems to be a promising alternative approach to AVS to the demonstration of lateralized aldosterone excess, but this technique requires a facility for the preparation of the tracer, which has a very short half-life, and therefore could only be developed at large tertiary referral centres (100). Whether <sup>11</sup>Cmethomidate positron emission tomography could identify the majority of APAs, which are quite small, remains to be proven. The same applies to use of a chemokine receptor type 4 (CXCR4)-specific ligand used for molecular imaging of APA in one study of only nine patients (101).

### **GENETIC TESTING**

An exome sequencing of 24 APA allowed the discovery of somatic mutations in the Kir3.4 gene encoding the KCNJ5K channel, which were thereafter identified in few families with bilateral adrenal hyperplasia causing drug-resistant

hypertension and requiring bilateral adrenalectomy (102). After this seminal report, other mutations were found which led to a novel classification of familial hyperaldosteronism, besides the glucocorticoid-remediable form known for some decades (under revision (76)). To date, genetic testing is performed for research purposes and is advised only for ruling out the need of AVS as discussed above. However, the recent report that APA with some KCNJ5 mutations respond to macrolides and their derivatives without antibiotic activity can open a new avenue toward personalized medical treatment of PA (103,104), a hypothesis that is being tested in the MAPA Study (105).

### **TREATMENT**

Laparoscopic adrenalectomy is currently the best treatment for PA patients with lateralized aldosterone excess. It can be performed during a short hospital stay at a very low operative risk (106–108). At our institution, we follow the recommendation from the Endocrine Society guidelines, that a lateralized aldosterone secretion should be demonstrated before undertaking surgery in patients who are candidates for general anaesthesia and wish to achieve long-term cure (41). In our hands, when guided by demonstration of lateralized aldosterone excess at AVS, unilateral laparoscopic adrenalectomy almost invariably provides correction of the biochemical changes of PA (21,87); and the cure rate of hypertension (patients who are cured or experience a marked improvement) is ~82% (21). Even when antihypertensive treatment cannot be withdrawn after adrenalectomy, the number and/or the doses of antihypertensive drugs can be markedly decreased and/or resistant hypertension can be resolved. Predictors of hypertension cure include young age, female sex, a short history of hypertension and no evidence of CV damage, including the absence of vascular remodelling (26,109) and renal chronic kidney disease (110). The wide variation of results in the literature is probably because at some centres adrenalectomy is performed on the basis of imaging alone that, as mentioned before, can be misleading in a substantial proportion of patients (111,112). Of interest, at a centre in Brisbane, Australia, adrenalectomy was also associated with a considerable improvement in several indexes of quality of life (113). Hence, the overall available evidence supports the concept that the sooner the diagnosis is made and adrenalectomy is performed, the better the outcome.

On the whole, the common reasons of failure to cure PA are an inaccurate diagnosis (AVS was not performed or its results were incorrectly interpreted) and, more frequently, the concurrence of primary hypertension and/or chronic kidney disease (114). As PA and primary (essential) hypertension are both highly prevalent, 20–30% of patients would be expected to have primary hypertension concurrent with PA, which cannot be cured by adrenalectomy.

For patients who are not candidates for surgery or do not show lateralized aldosterone excess, mineralocorticoid receptor antagonists, such as spironolactone, canrenone, potassium canrenoate and eplerenone (which is more selective, but also more expensive, weaker and shorter acting than the other antagonists and is not generally available) are a reasonable alternative to adrenalectomy. Novel potent and specific mineralocorticoid receptor antagonists are also being developed (115). Results from pilot studies suggest



that these novel antagonists can effectively control blood pressure in patients with PA and decrease left ventricular mass. Whether they are as effective as adrenalectomy in reversing damage to the target organs (such as the kidneys and heart) remains to be conclusively proven. Gynecomastia and impotence, which are not rare in men receiving mineralocorticoid receptor antagonists for a long time, are dose-dependent side effects. Hence, the use of reduced doses in combination, if necessary, with other agents, such as long-acting calcium channel blockers (some of which also have mineralocorticoid antagonistic properties) (115) can minimize these side effects. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers can be particularly useful, as they effectively control the stimulation of the renin-angiotensin system by the diuretic action of the mineralocorticoid receptor antagonists. Although the latter agents can effectively control hyperaldosteronism, but do not cure it, aldosterone synthase inhibitors are also being developed and tested in phase III trials, albeit with limited success to date (66).

## CONCLUSIONS

By following a few simple rules, most physicians dealing with hypertensive patients can successfully and cost-effectively identify many patients with so-called 'essential' hypertension whose high blood pressure is instead caused by PA. Hyperaldosteronism and hypokalaemia are curable with adrenalectomy in almost all patients, and blood pressure can also be normalized or considerably reduced in a substantial proportion of these patients when a unilateral cause of PA is discovered. Hence, screening for PA is beneficial, particularly when hypertension is severe and/or resistant to treatment, because removal of an APA can bring blood pressure under control even with the withdrawal of a prominent reduction in the number and dosage of anti-hypertensive medications.

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## REFERENCES

- Rossi GP. Prevalence and diagnosis of primary aldosteronism. *Curr Hypertens Rep* 2010; 12: 342–348.
- Conn JW. Plasma renin activity in primary aldosteronism. *JAMA* 1964; 190: 222–225.
- Conn JW. Part I. Painting background. Part II. Primary aldosteronism, a new clinical syndrome. *J Lab Clin Med* 1990; 116: 253–267.
- Fritsch NM, Schiffrin EL, Neves MF, Schiffrin EL. Aldosterone: A risk factor for vascular disease. *Curr Hypertens Rep* 2003; 5: 59–65.
- Pu Q, Neves MF, Virdis A et al. Endothelin antagonism on aldosterone-induced oxidative stress and vascular remodeling. *Hypertension* 2003; 42: 49–55.
- Schupp N, Queisser N, Wolf M et al. Aldosterone causes DNA strand breaks and chromosomal damage in renal cells, which are

prevented by mineralocorticoid receptor antagonists. *Horm Metab Res* 2010; 42(6): 458–465.

- Rocha R, Rudolph AE, Friedrich GE et al. Aldosterone induces a vascular inflammatory phenotype in the rat heart. *Am J Physiol Heart Circ Physiol* 2002; 283: H1802–H1810.
- Weber KT, Brilla CG, Campbell SE, Reddy HK. Myocardial fibrosis and the concepts of cardioprotection and cardioreparation. *J Hypertens Suppl* 1992; 10: S87–S94.
- Brilla CG, Pick R, Tan LB et al. Remodeling of the rat right and left ventricles in experimental hypertension. *Circ Res* 1990; 67: 1355–1364.
- Rossi GP, Sacchetto A, Pavan E et al. Remodeling of the left ventricle in primary aldosteronism due to Conn's adenoma. *Circulation* 1997; 95: 1471–1478.
- Rossi GP, Bello VD, Ganzaroli C et al. Excess aldosterone is associated with alterations of myocardial texture in primary aldosteronism. *Hypertension* 2002; 40: 23–27.
- Farquharson CA, Struthers AD. Aldosterone induces acute endothelial dysfunction *in vivo* in humans: Evidence for an aldosterone-induced vasculopathy. *Clin Sci (Lond)* 2002; 103: 425–431.
- Nishizaka MK, Zaman MA, Green SA et al. Impaired endothelium-dependent flow-mediated vasodilation in hypertensive subjects with hyperaldosteronism. *Circulation* 2004; 109: 2857–2861.
- Taddei S, Virdis A, Mattei P, Salvetti A. Vasodilation to acetylcholine in primary and secondary forms of human hypertension. *Hypertension* 1993; 21: 929–933.
- Muiesan ML, Rizzoni D, Salvetti M et al. Structural changes in small resistance arteries and left ventricular geometry in patients with primary and secondary hypertension. *J Hypertens* 2002; 20: 1439–1444.
- Rizzoni D, Muiesan ML, Porteri E et al. Relations between cardiac and vascular structure in patients with primary and secondary hypertension. *J Am Coll Cardiol* 1998; 32: 985–992.
- Halimi JM, Mimran A. Albuminuria in untreated patients with primary aldosteronism or essential hypertension. *J Hypertens* 1995; 13: 1801–1802.
- Rossi GP, Bernini G, Desideri G et al. Renal damage in primary aldosteronism: Results of the PAPY Study. *Hypertension* 2006; 48: 232–238.
- Rossi GP, Sechi LA, Giacchetti G et al. Primary aldosteronism: Cardiovascular, renal and metabolic implications. *Trends Endocrinol Metab* 2008; 19: 88–90.
- Milliez P, Girerd X, Plouin PF, Blacher J, Safar ME, Mourad JJ. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. *J Am Coll Cardiol* 2005; 45: 1243–1248.
- Rossi GP, Cesari M, Cuspidi C et al. Long-term control of arterial hypertension and regression of left ventricular hypertrophy with treatment of primary aldosteronism. *Hypertension* 2013; 62: 62–69.
- Rossi GP. Primary aldosteronism: A needle in a haystack or a yellow cab on Fifth Avenue? *Curr Hypertens Rep* 2004; 6: 1–4.
- Conn JW. A concluding response. *Arch Intern Med* 1969; 123: 154–155.
- Rossi GP, Pessina AC, Heagerty AM. Primary aldosteronism: An update on screening, diagnosis and treatment. *J Hypertens* 2008; 26: 613–621.
- Gordon RD, Ziesak MD, Tunny TJ et al. Evidence that primary aldosteronism may not be uncommon: 12% incidence among antihypertensive drug trial volunteers. *Clin Exp Pharmacol Physiol* 1993; 20: 296–298.
- Gordon RD, Stowasser M, Tunny TJ et al. High incidence of primary aldosteronism in 199 patients referred with hypertension. *Clin Exp Pharmacol Physiol* 1994; 21: 315–318.
- Rossi GP, Bernini G, Caliumi C et al. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. *J Am Coll Cardiol* 2006; 48: 2293–2300.
- Conn J, Cohen E, Rovner D, Nesbit R. Normokalemic primary aldosteronism. A detectable cause of curable 'Essential' hypertension. *JAMA* 1965; 193: 200–206.
- Mulatero P, Monticone S, Burrello J et al. Guidelines for primary aldosteronism. *J Hypertens* 2016; 34: 2253–2257.
- Monticone S, Burrello J, Tizzani D et al. Prevalence and clinical manifestations of primary aldosteronism encountered in primary care practice. *J Am Coll Cardiol* 2017; 69: 1811–1820.
- Maiolino G, Calò LA, Rossi GP. The time has come for systematic screening for primary aldosteronism in all hypertensives. *J Am Coll Cardiol* 2017; 69: 1821–1823.
- Rossi GP, Gioco F, Fassina A, Gomez-Sanchez CE. Normoaldosteronemic aldosterone-producing adenoma:



- Immunochemical characterization and diagnostic implications. *J Hypertens* 2015; 33: 2546–2549.
33. Conn JW, Cohen EL, Herwig KR. Primary aldosteronism: A non-invasive procedure for tumor localization as well as for distinction from bilateral hyperplasia. *Adv Nephrol Necker Hosp* 1977; 7: 137–156.
  34. Nishikawa T, Omura M. Clinical characteristics of primary aldosteronism: Its prevalence and comparative studies on various causes of primary aldosteronism in Yokohama Rosai Hospital. *Biomed Pharmacother* 2000; 54(Suppl. 1): 83s–85s.
  35. Rossi E, Regolisti G, Negro A et al. High prevalence of primary aldosteronism using postcaptopril plasma aldosterone to renin ratio as a screening test among Italian hypertensives. *Am J Hypertens* 2002; 15: 896–902.
  36. Calhoun DA, Nishizaka MK, Zaman MA et al. Hyperaldosteronism among black and white subjects with resistant hypertension. *Hypertension* 2002; 40: 892–896.
  37. Lim PO, Dow E, Brennan G et al. High prevalence of primary aldosteronism in the Tayside hypertension clinic population. *J Hum Hypertens* 2000; 14: 311–315.
  38. Rayner BL, Myers JE, Opie LH et al. Screening for primary aldosteronism—normal ranges for aldosterone and renin in three South African population groups. *South African Med Journal* 2001; 91: 594–599.
  39. Olivieri O, Ciacciarelli A, Signorelli D et al. Aldosterone to Renin ratio in a primary care setting: The Bussolengo study. *J Clin Endocrinol Metab* 2004; 89: 4221–4226.
  40. Rossi GP, Seccia TM, Pessina AC. Clinical use of laboratory tests for the identification of secondary forms of arterial hypertension. *Crit Rev Clin Lab Sci* 2007; 44: 1–85.
  41. Funder JW, Carey RM, Mantero F et al. The management of primary aldosteronism: Case detection, diagnosis, and treatment: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2016; 101: 1889–1916.
  42. Funder JW, Carey RM, Fardella C et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2008; 93: 3266–3281.
  43. Douma S, Petidis K, Doumas M et al. Prevalence of primary hyperaldosteronism in resistant hypertension: A retrospective observational study. *Lancet* 2008; 371: 1921–1926.
  44. Omata K, Yamazaki Y, Nakamura Y et al. Genetic and histopathologic intertumor heterogeneity in primary aldosteronism. *J Clin Endocrinol Metab* 2017; 102: 1792–1796.
  45. Rossi GP, Funder JW. Adrenal vein sampling is the preferred method to select patients with primary aldosteronism for adrenalectomy response to adrenal vein sampling is the preferred method to select patients with primary aldosteronism for adrenalectomy: Pro side of the argument. *Hypertension* 2018; 71: 5–9.
  46. Cuspidi C, Ambrosioni E, Mancia G et al. Role of echocardiography and carotid ultrasonography in stratifying risk in patients with essential hypertension: The Assessment of Prognostic Risk Observational Survey. *J Hypertens* 2002; 20: 1307–1314.
  47. Hiramatsu K, Yamada T, Yukimura Y et al. A screening test to identify aldosterone-producing adenoma by measuring plasma renin activity. Results in hypertensive patients. *Arch Intern Med* 1981; 141: 1589–1593.
  48. Rossi GP, Ceolotto G, Rossitto G et al. Prospective validation of an automated chemiluminescence-based assay of renin and aldosterone for the work-up of arterial hypertension. *Clin Chem Lab Med* 2016; 54: 1441–1450.
  49. Rossi GP, Seccia TM, Pessina AC. A diagnostic algorithm—the holy grail of primary aldosteronism. *Nat Rev* 2011; 7: 697–699.
  50. Rossi GP, Rossi E, Pavan E et al. Screening for primary aldosteronism with a logistic multivariate discriminant analysis. *Clin Endocrinol (Oxf)* 1998; 49: 713–723.
  51. Rossi GP, Bisogni V. The Aldosterone Renin Ratio (ARR) APP as tool to enhance the detection rate of primary aldosteronism. *High Blood Press Cardiovasc Prev* 2016; 23: 147–149.
  52. Rossi GP, Seccia TM, Palumbo G et al. Within-patient reproducibility of the aldosterone: Renin ratio in primary aldosteronism. *Hypertension* 2010; 55: 83–89.
  53. Maiolino G, Rossitto G, Bisogni V et al. Quantitative value of aldosterone-renin ratio for detection of aldosterone-producing adenoma: The aldosterone-renin ratio for primary aldosteronism (AQUARR) study. *J Am Heart Assoc* 2017; 6: e005574.
  54. Mulatero P, Rabbia F, Milan A et al. Drug effects on aldosterone/plasma renin activity ratio in primary aldosteronism. *Hypertension* 2002; 40: 897–902.
  55. Stowasser M, Gordon RD, Rutherford JC et al. Diagnosis and management of primary aldosteronism. *J Renin Angiotensin Aldosterone Syst* 2001; 2: 156–169.
  56. Agharazii M, Douville P, Grose JH, Lebel M. Captopril suppression versus salt loading in confirming primary aldosteronism. *Hypertension* 2001; 37: 1440–1443.
  57. Castro OL, Yu X, Kem DC. Diagnostic value of the post-captopril test in primary aldosteronism. *Hypertension* 2002; 39: 935–938.
  58. Rossi GP, Barisa M, Belfiore A et al. The aldosterone-renin ratio based on the plasma renin activity and the direct renin assay for diagnosing aldosterone-producing adenoma. *J Hypertens* 2010; 28: 1892–1899.
  59. Rossitto G, Cesari M, Ceolotto G, Maiolino G, Maria T, Rossi GP, Rossi GP. Effects of mineralocorticoid and AT-1 receptor antagonism on the aldosterone–renin ratio (ARR) in primary aldosteronism patients (EMIRA Study): rationale and design. *J Hum Hypertens* [Internet]. 2018; Available from: <http://dx.doi.org/10.1038/s41371-018-0139-x>
  60. Williams B, Mancia G, Spiering W et al. Practice Guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology ESH/ESC Task Force for the Management of Arterial Hypertension. *J Hypertens* 2018;36:2284–2309.
  61. Irony I, Kater CE, Biglieri EG, Shackleton CH. Correctable subsets of primary aldosteronism. Primary adrenal hyperplasia and renin responsive adenoma. *Am J Hypertens* 1990; 3: 576–582.
  62. Gordon RD, Gomez-Sanchez CE, Hamlet SM et al. Angiotensin-responsive aldosterone-producing adenoma masquerades as idiopathic hyperaldosteronism (IHA: Adrenal hyperplasia) or low-renin essential hypertension. *J Hypertens* 1987; 5: S103–S106.
  63. Holland OB, Brown H, Kuhnert L et al. Further evaluation of saline infusion for the diagnosis of primary aldosteronism. *Hypertension* 1984; 6: 717–723.
  64. Rossi GP, Belfiore A, Bernini G et al. Prospective evaluation of the saline infusion test for excluding primary aldosteronism due to aldosterone-producing adenoma. *J Hypertens* 2007; 25: 1433–1442.
  65. Rossi GP, Belfiore A, Bernini G et al. Comparison of the captopril and the saline infusion test for excluding aldosterone-producing adenoma. *Hypertension* 2007; 50: 424–431.
  66. Amar L, Azizi M, Menard J et al. Aldosterone synthase inhibition with LCI699. *Hypertension* 2010; 56: 831–838.
  67. Funder JW, Rossi GP. Adrenal vein sampling versus CT scanning in primary aldosteronism. *Lancet Diabetes Endocrinol* 2016; 4: 886.
  68. Nishikawa T, Omura M, Satoh F et al. Guidelines for the diagnosis and treatment of primary aldosteronism—The Japan Endocrine Society 2009. *Endocr J* 2011; 58: 711–721.
  69. Young WF, Stanson AW, Thompson GB et al. Role for adrenal venous sampling in primary aldosteronism. *Surgery* 2004; 136: 1227–1235.
  70. Nishimura M, Uzu T, Fujii T et al. Cardiovascular complications in patients with primary aldosteronism. *Am J Kidney Dis* 1999; 33: 261–266.
  71. Brilla CG, Maisch B, Weber KT. Myocardial collagen matrix remodelling in arterial hypertension. *Eur Heart J* 1992; 13(Suppl. D): 24–32.
  72. Takeda R, Matsubara T, Miyamori I et al. Vascular complications in patients with aldosterone producing adenoma in Japan: Comparative study with essential hypertension. The Research Committee of Disorders of Adrenal Hormones in Japan. *J Endocrinol Invest* 1995; 18: 370–373.
  73. Daunt N. Adrenal vein sampling: How to make it quick, easy, and successful. *Radiographics* 2005; 25(Suppl. 1): S143–S158.
  74. Rossi GP, Auchus RJ, Brown M et al. An expert consensus statement on use of adrenal vein sampling for the subtyping of primary aldosteronism. *Hypertension* 2014; 63: 151–160.
  75. Lim V, Guo Q, Grant CS et al. Accuracy of adrenal imaging and adrenal venous sampling in predicting surgical cure of primary aldosteronism. *J Clin Endocrinol Metab* 2014; 99: 2712–2719.
  76. Lenzini L, Rossi GP. The molecular basis of primary aldosteronism: From chimeric gene to channelopathy. *Curr Opin Pharmacol* 2015; 21: 35–42. (under revision)
  77. Lenzini L, Prisco S, Caroccia B, Rossi GP. Saga of Familial Hyperaldosteronism. *Hypertension*. 2018;71:1010–1014.
  78. Rossi GP, Pitter G, Bernante P et al. Adrenal vein sampling for primary aldosteronism: The assessment of selectivity and lateralization of aldosterone excess baseline and after adrenocorticotrophic hormone (ACTH) stimulation. *J Hypertens* 2008; 26: 989–997.
  79. Rossitto G, Battistel M, Barbiero G et al. The subtyping of primary aldosteronism by adrenal vein sampling: Sequential blood

- sampling causes factitious lateralization. *J Hypertens* 2018; 36: 335–343.
80. Rossi GP, Vendraminelli R, Cesari M, Pessina AC. A thoracic mass with hypertension and hypokalaemia. *Lancet* 2000; 356: 1570.
  81. Miotto D, Toni RD, Pitter G et al. Impact of accessory hepatic veins on adrenal vein sampling for identification of surgically curable primary aldosteronism. *Hypertension* 2009; 54: 885–889.
  82. Omura K, Ota H, Takahashi Y et al. Anatomical variations of the right adrenal vein. *Hypertension* 2017; 69: 428–434.
  83. Mengozzi G, Rossato D, Bertello C et al. Rapid cortisol assay during adrenal vein sampling in patients with primary aldosteronism. *Clin Chem* 2007; 53: 1968–1971.
  84. Auchus RJ, Michaelis C, Wians FH Jr et al. Rapid cortisol assays improve the success rate of adrenal vein sampling for primary aldosteronism. *Ann Surg* 2009; 249: 318–321.
  85. Rossi GP, Sacchetto A, Chiesura-Corona M et al. Identification of the etiology of primary aldosteronism with adrenal vein sampling in patients with equivocal computed tomography and magnetic resonance findings: Results in 104 consecutive cases. *J Clin Endocrinol Metab* 2001; 86: 1083–1090.
  86. Seccia TM, Miotto D, Toni RD et al. Adrenocorticotrophic hormone stimulation during adrenal vein sampling for identifying surgically curable subtypes of primary aldosteronism: Comparison of 3 different protocols. *Hypertension* 2009; 53: 761–766.
  87. Rossitto G, Maiolino G, Lenzi L et al. Subtyping of primary aldosteronism with adrenal vein sampling: Hormone- and side-specific effects of cosyntropin and metoclopramide. *Surgery* 2018; 163(4): 789–795.
  88. Deinum J, Groenewoud H, Jan van der W Lenzini L, Rossi GP: Adrenal venous sampling: Cosyntropin stimulation or not? For. The case for using cosyntropin during AVS. Against. The case against using cosyntropin during AVS. *Eur J Endocrinol* 2019: in press.
  89. Enberg U, Volpe C, Hoog A et al. Postoperative differentiation between unilateral adrenal adenoma and bilateral adrenal hyperplasia in primary aldosteronism by mRNA expression of the gene CYP11B2. *Eur J Endocrinol* 2004; 151: 73–85.
  90. Nishimoto K, Nakagawa K, Li D et al. Adrenocortical zonation in humans under normal and pathological conditions. *J Clin Endocrinol Metab* 2010; 95: 2296–2305.
  91. Rossi GP, Barisa M, Allolio B et al. The Adrenal Vein Sampling International Study (AVIS) for identifying the major subtypes of primary aldosteronism. *J Clin Endocrinol Metab* 2012; 97: 1606–1614.
  92. Dekkers T, Prejbisz A, Kool LJ et al. Adrenal vein sampling versus CT scan to determine treatment in primary aldosteronism: An outcome-based randomised diagnostic trial. *Lancet Diabetes Endocrinol* 2016; 4: 739–746.
  93. Letavernier E, Peyrard S, Amar L et al. Blood pressure outcome of adrenalectomy in patients with primary hyperaldosteronism with or without unilateral adenoma. *J Hypertens* 2008; 26: 1816–1823.
  94. Zarnegar R, Young WF Jr, Lee J et al. The aldosteronoma resolution score: Predicting complete resolution of hypertension after adrenalectomy for aldosteronoma. *Ann Surg* 2008; 247: 511–518.
  95. Rossi GP, Funder JW. Adrenal venous sampling versus computed tomographic scan to determine treatment in primary aldosteronism (The SPARTACUS Trial): A critique. *Hypertension* 2017; 69: 396–397.
  96. Williams TA, Lenders JWM, Mulatero P et al. Outcomes after adrenalectomy for unilateral primary aldosteronism: An international consensus on outcome measures and analysis of remission rates in an international cohort. *Lancet Diabetes Endocrinol* 2017; 5: 858–867.
  97. Mahtani KR. ‘Spin’ in reports of clinical research. *Evid Based Med* 2016; 21: 2016–2018.
  98. Williams TA, Burrello J, Sechi LA et al. Computed tomography and adrenal venous sampling in the diagnosis of unilateral primary aldosteronism. *Hypertension*. 2018;72:641–649.
  99. Rossi GP, Rossitto G, Amar L, Azizi M, et al. The Outcomes of Subtyped Primary Aldosteronism Patients in the AVIS-2 Study. Submitted.
  100. Burton TJ, Mackenzie IS, Balan K et al. Evaluation of the sensitivity and specificity of (11)C-metomidate positron emission tomography (PET)-CT for lateralizing aldosterone secretion by Conn’s adenomas. *J Clin Endocrinol Metab* 2012; 97: 100–109.
  101. Heinze B, Fuss CT, Mulatero P et al. Targeting CXCR4 (CXC Chemokine Receptor Type 4) for molecular imaging of aldosterone-producing adenoma. *Hypertension* 2018; 71: 317–325.
  102. Choi M, Scholl UI, Yue P et al. K+ channel mutations in adrenal aldosterone-producing adenomas and hereditary hypertension. *Science* 2011; 331: 768–772.
  103. Scholl UI, Abriola L, Zhang C et al. Macrolides selectively inhibit mutant KCNJ5 potassium channels that cause aldosterone-producing adenoma. *J Clin Invest* 2017; 127: 2739–2750.
  104. Caroccia B, Prisco S, Seccia TM et al. Macrolides blunt aldosterone biosynthesis: A proof-of-concept study in KCNJ5 mutated adenoma cells ex vivo. *Hypertension* 2017; 70: 1238–1242.
  105. Maiolino G, Ceolotto G, Battistel M et al. Macrolides for KCNJ5-mutated Aldosterone-Producing Adenoma (MAPA): A study of personalized diagnosis of primary aldosteronism with implications for treatment. *Blood Press* 2018; 27(4): 200–205.
  106. Toniato A, Bernante P, Rossi GP et al. Laparoscopic versus open adrenalectomy: Outcome in 35 consecutive patients. *Int J Surg Invest* 2000; 1: 503–507.
  107. Jeschke K, Janetschek G, Peschel R et al. Laparoscopic partial adrenalectomy in patients with aldosterone-producing adenomas: Indications, technique, and results. *Urology* 2003; 61: 69–72.
  108. Meria P, Kempf BF, Hermieu JF et al. Laparoscopic management of primary hyperaldosteronism: Clinical experience with 212 cases. *J Urol* 2003; 169: 32–35.
  109. Rossi GP, Bolognesi M, Rizzoni D et al. Vascular remodeling and duration of hypertension predict outcome of adrenalectomy in primary aldosteronism patients. *Hypertension* 2008; 51: 1366–1371.
  110. Obara T, Ito Y, Okamoto T et al. Risk factors associated with postoperative persistent hypertension in patients with primary aldosteronism. *Surgery* 1992; 112: 987–993.
  111. Sawka AM, Young WF, Thompson GB et al. Primary aldosteronism: Factors associated with normalization of blood pressure after surgery. *Ann Intern Med* 2001; 135: 258–261.
  112. Lumachi F, Ermani M, Basso SM et al. Long-term results of adrenalectomy in patients with aldosterone-producing adenomas: Multivariate analysis of factors affecting unresolved hypertension and review of the literature. *Am Surg* 2005; 71: 864–869.
  113. Sukor N, Kovgovek C, Gordon RD et al. Improved quality of life, blood pressure, and biochemical status following laparoscopic adrenalectomy for unilateral primary aldosteronism. *J Clin Endocrinol Metab* 2010; 95: 1360–1364.
  114. Proye CA, Mulliez EA, Carnaille BM et al. Essential hypertension: First reason for persistent hypertension after unilateral adrenalectomy for primary aldosteronism? *Surgery* 1998; 124: 1128–1133.
  115. Dietz JD, Du S, Bolten CW et al. A number of marketed dihydropyridine calcium channel blockers have mineralocorticoid receptor antagonist activity. *Hypertension* 2008; 51: 742–748.

# PHEOCHROMOCYTOMA AND PARAGANGLIOMA

# 63

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## INTRODUCTION

The terminology of chromaffin cell tumours is sometimes confusing when pheochromocytoma and paraganglioma are interchangeably used. The term pheochromocytoma should be reserved for chromaffin cell tumours of the adrenal gland, while the term paraganglioma should be used for extra-adrenal chromaffin cell tumours. This distinction is clinically relevant because these tumours not only differ in location but also in clinical presentation, genetic background and malignant potential.

Pheochromocytomas arise from the adrenal medulla (80–85%), while sympathetic paragangliomas arise from chromaffin cells associated with the paravertebral ganglia of the sympathetic chain (15–20%). Paragangliomas can also originate from cells associated with the parasympathetic nervous system, and these tumours are usually located in the neck and skull base (1).

The degree and patterns of catecholamine secretion largely account for the clinical presentation and hemodynamic features. About half of adrenal tumours produce a combination of noradrenaline and adrenaline, and the other half nearly exclusively noradrenaline (2,3). In contrast, most paragangliomas (PPGLs) located in the thorax, abdomen and pelvis produce exclusively noradrenaline. This is due to the lack in extra-adrenal chromaffin tissue of the enzyme PNMT that converts noradrenaline into adrenaline. Other paragangliomas produce a mixture of noradrenaline and dopamine and some exclusively dopamine (2,3). The paragangliomas located in the neck and skull base are typically hormonally inactive except for mild production of dopamine and rarely noradrenaline (1).

Because pheochromocytomas and PPGLs are rare and may have severe and even fatal cardiovascular consequences, the clinician needs a high awareness and early consideration of the presence of such tumour. When correctly diagnosed and treated, most of PPGLs are curable. When undiagnosed or improperly treated, they can have fatal consequences. In contrast, when a PPGL is diagnosed and managed by a highly experienced clinical team, the tumour can be successfully resected with minimal perioperative mortality (4,5).

## PREVALENCE

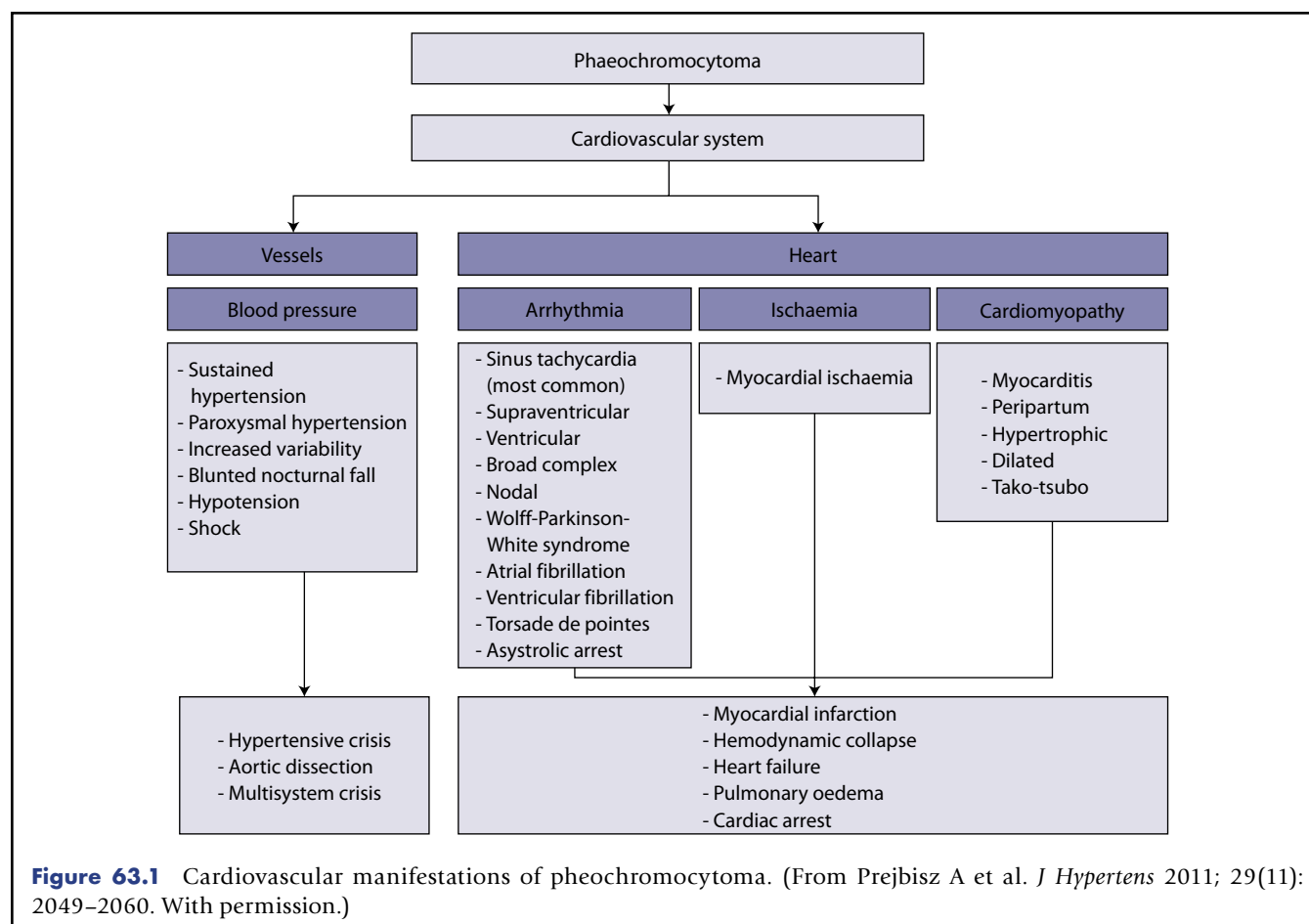
The prevalence of PPGLs in hypertensive populations is low (0.2–0.6%), but higher in selected patient groups such as those with an adrenal incidentalomas (5%) (1,3,4,6–8). A recent study from the Netherlands showed that, probably due to more intensified diagnostics, the age-standardized incidence rate has increased over the last two decades by nearly 50%. As PPGLs may also go unrecognized, its prevalence in autopsy studies is 0.05% (1,3,4,6–10).

In children with hypertension, the prevalence of PPGL is approximately 1.7% and PPGLs more frequently have a hereditary background (70%). Recently, in a large group of patients it has been demonstrated that children show higher prevalence than adults of hereditary (80% vs. 53%), extra-adrenal (66% vs. 35%), multifocal (33% vs. 13.5%), metastatic (49.5% vs. 29%) and recurrent (29.5% vs. 14%) PPGLs (11).

## CLINICAL PRESENTATION

The clinical presentations of PPGLs are highly variable, leading to its designation as the ‘great mimic’, or ‘the disease with the multiple faces’ (12,13). There are numerous reports in the literature of highly unusual presentations of PPGLs. Some patients may be completely asymptomatic, while in others PPGL can be confused with many other disorders that display similar cardiovascular, abdominal, neurologic or metabolic signs and symptoms.

Excessive production and high levels of circulating catecholamines are responsible for the classical symptoms of hyperadrenergic spells, including tachycardia, headache and sweating, which may occur spontaneously or may be provoked by different physical or chemical triggers (e.g. general anaesthesia, medications and other) (1,3,4). The frequency of spells may vary from several times per day to a few times per month. The episodes may occur suddenly and unexpectedly – in 80% of the cases they commonly last less than 1 hour, then subside gradually and lead to exhaustion of the patient.



Recent studies have shown that the classic triad occurs more rarely than usually assumed. Diabetes and weight loss are other signs of the hyperadrenergic state (1,3,4). The excessive adrenergic stimulation of the cardiovascular system may produce paroxysmal hypertension, which appears to be less frequent than observed in previous studies. Approximately one-half of patients have sustained hypertension, whereas the other 50% suffer from paroxysmal hypertension. Normotension is typical for head and neck paragangliomas (1). Because catecholamines can inhibit peristalsis, PPGL may be associated with severe constipation and even enteric pseudo-obstruction or ileus. Mesenteric arterial vasoconstriction due to excessive catecholamines may result in ischaemic enterocolitis with intestinal necrosis (4).

PPGLs can present with a plethora of life-threatening cardiovascular manifestations, including hypertensive crisis, myocardial infarction, shock and multisystem failure (Figure 63.1). Most of these life-threatening cardiovascular presentations of PPGLs result from a rapid and massive release of catecholamines from the tumour (8,14–16).

Rarely, patients with a PPGL present with low blood pressure or even shock that may then precede a multisystem crisis. Sinus tachycardia with palpitations as the presenting symptom is the most prevalent abnormality of cardiac rhythm in PPGL, but tumours can also be associated with more serious ventricular arrhythmias or conduction disturbances (8). Reversible dilated or hypertrophic cardiomyopathy are other well-established cardiac manifestations of

PPGL, with more recent attention to an increasing number of cases with Tako-Tsubo cardiomyopathy (8,17,18).

In addition to catecholamine excess, PPGLs have been found very rarely to secrete neuropeptide Y, chromogranin A, vasointestinal peptide, serotonin, calcitonin, parathyroid hormone-related protein, adrenocorticotrophic hormone or interleukin-64. This can result in typical clinical features related to these hormones, for example, diarrhoea in the case of vasointestinal peptide secretion.

Finally, some patients can present with a metastatic PPGL with symptoms resulting from tumour infiltration and distant metastatic lesions (e.g. bone pain in the case of osseous metastasis).

Symptoms of catecholamine excess can be further mimicked by hyperthyroidism, panic attacks, hypoglycaemia and alcohol withdrawal symptoms, and these conditions should therefore be considered in patients with spells suggestive of excessive catecholamine production. Sudden cessation of clonidine or beta-blocker therapy may also cause PPGL-like symptoms due to the rebound effect of catecholamines (1,3,4,7).

### WHICH PATIENTS SHOULD BE SCREENED FOR PPGL?

Clinicians should base their decision for biochemical screening for a PPGL on signs and symptoms or other tumour



**Table 63.1** Signs and symptoms of pheochromocytoma

| Sign/symptoms                       | Frequency <sup>a</sup> |
|-------------------------------------|------------------------|
| <i>Signs</i>                        |                        |
| Hypertension                        | ++++                   |
| Sustained hypertension              | ++                     |
| Paroxysmal hypertension             | ++                     |
| Postural hypotension                | ++                     |
| Tachycardia or reflex bradycardia   | +++                    |
| Pallor                              | ++                     |
| Flushing (rare)                     | +                      |
| Weight loss                         | +                      |
| Fasting hyperglycaemia              | ++                     |
| Decreased gastrointestinal motility | +                      |
| Increased respiratory rate          | +                      |
| Psychosis                           | +                      |
| <i>Symptoms</i>                     |                        |
| Headaches                           | ++++                   |
| Palpitations                        | ++++                   |
| Excessive sweating                  | ++++                   |
| Anxiety/nervousness                 | +++                    |
| Tremulousness                       | ++                     |
| Pain in chest/abdomen               | ++                     |
| Weakness, fatigue                   | ++                     |
| Nausea/vomiting                     | ++                     |
| Dizziness or faintness              | +                      |
| Paresthesias                        | +                      |
| Constipation (rarely diarrhoea)     | +                      |
| Visual disturbances                 | +                      |

Source: From Eisenhofer G et al. *Drug Saf* 2007; 30(11): 1031–162. With permission.

<sup>a</sup> Highest (+++++) to lowest (+) frequency.

manifestations, or clinical settings that suggest the possibility of excessive catecholamine production (Table 63.1). Any even remote suspicion of PPGL should prompt biochemical testing, irrespective of blood pressure level, particularly when there are paroxysms that occur spontaneously or are provoked by anaesthesia, surgery or medications, because complications of PPGLs can be life-threatening (1,3,8). Early consideration, confirmation, and treatment of PPGLs is rewarding, since a timely diagnosis and appropriate treatment significantly reduce morbidity and mortality (3,4).

Among precipitating factors, medications and drugs known to provoke catecholamine release from the tumour

can provide particularly useful clues to the possibility of an underlying PPGL (1,2,19). In any case of sustained paroxysmal hypertension or paradoxical hypertension despite antihypertensive therapy, especially during therapy with beta-blockers, the possibility of a PPGL has to be kept in mind and ruled out (1,2,20).

In addition to the above considerations, any knowledge gained from the patient or family members for the presence of a mutation in a PPGL tumour-susceptibility gene should arouse strong suspicion that the patient may harbour a catecholamine-producing tumour. In addition, a symptomatic patient with a history of PPGL should be screened for a new or recurrent tumour (8,16).

Other situations in which a PPGL should be strongly suspected pertain to those patients in whom compression of an unsuspected catecholamine-producing tumour causes signs and/or symptoms of catecholamine excess. Such situations include pregnancy, childbirth and micturition-induced hypertensive episodes (e.g. in the case of a urinary bladder paraganglioma) (1–3,20). Finally, screening for PPGLs should also be performed in all asymptomatic patients with an incidentally discovered adrenal mass or who are at increased risk due to hereditary predisposition or a previous history of PPGLs (21).

## BIOCHEMICAL TESTING

With the remarkable advancement in biochemical techniques during the past decades, the physician now has the possibility to establish the diagnosis of PPGL more reliably and rapidly. Biochemical testing should precede expensive imaging procedures and choosing the most appropriate laboratory test is crucial for reliable detection or exclusion of the tumour (1,2,20,22). As recommended in the Endocrine Society Clinical Practice Guideline for PPGLs, initial biochemical testing should include measurements of plasma-free or urine-fractionated metanephrines. There is no evidence so far that one test is superior to the other (1). Inclusion of plasma 3-methoxytyramine (MTY), the metabolite of dopamine, only modestly improves detection of PPGLs above that achieved using standard measurements of normetanephrine and metanephrine. Measurement of MTY is also useful for detection of dopamine producing head and neck paragangliomas (HNPPGLs) and for identifying metastatic PPGLs (23,24). Other available classical biochemical tests such as plasma or urinary catecholamines or urinary vanillyl-mandelic acid have inferior diagnostic value as compared to metanephrines (1).

Developments in assay technology over the past years shifted to liquid chromatographic–based methods such as liquid chromatography with electrochemical detection (LC-ECD) or tandem mass spectrometry (LC-MS/MS). The latter method is the method of first choice if available (2,20).

There are several important factors to be taken into account for correct interpretation of biochemical test results. It should be remembered that elevated plasma levels of metanephrines are not specific for PPGLs and, although much less than for catecholamines, they may also reflect increased sympathetic activity (1,2,20,22).

Several important preanalytical factors may impact on test results, including posture, exercise, stress, food and



medications, which may alter the production or clearance of catecholamines and their metabolites. For measurements of plasma metanephrines, a blood sample should be drawn with the patient in the supine position for at least 20 minutes of rest. In addition, reference intervals established in the same position should be used to obtain optimal sensitivity and specificity. The reliability of measurements of plasma-free metanephrines for the diagnosis of PPGL is dependent on the use of properly established reference intervals, which may differ between laboratories (2,20). For measurements of 24-hour urinary excretion of fractionated metanephrines, urinary creatinine can be used to verify completeness of the urine collection (1,22).

Because of the very high sensitivities of measurements of plasma-free and urine-fractionated metanephrines, normal values for these tests exclude PPGL with high reliability. Rarely, very small tumours (<1 cm) in usually asymptomatic patients result in normal levels of plasma or urinary metanephrines. Even more rare are tumours, in particular with a specific hereditary background, that do not produce metanephrines at all.

The most common causes of false-positive results for measurements of plasma metanephrines include inappropriate blood sampling conditions associated with sympathoadrenal activation. This particularly refers to sampling performed with the patient in the seated rather than the supine position (1,2,20,22). Analytical interference by drugs or their metabolites may cause false-positive test results, but this depends on the assay method used. With LC-MS/MS assay technology analytical interference is exceptional, while using the LC-ECD method several drugs may cause such interference, including acetaminophen, labetalol and methyl dopa. Other drugs responsible for false-positive test results cause pharmacodynamical interference such as cocaine, tricyclic antidepressants and MAO-inhibitors (2,20,22) (Table 63.2).

To avoid any false-positive test result of metanephrines, it would be ideal to discontinue all medications in each patient but that is not feasible in all patients from the practical point of view. An alternative option is to discontinue medications before sampling only if the initial test results are elevated (2,20,22).

Dietary factors are another source of potential false-positive test results that has frequently been mentioned. Indeed, several food products containing large amounts of biogenic amines such as banana, pineapple, nuts and cereals may increase the levels of metanephrines, but not to such extent that they cause false-positive test results. Dietary restriction of consuming food products containing biogenic amines is only indicated for the measurement of the dopamine metabolite MTY (22).

All patients with positive test results should receive appropriate follow-up according to the clinical presentation and magnitude of increased values. Additional testing such as the clonidine suppression test is indicated in those cases with borderline elevated test results that cannot be explained by faulty sampling conditions or patient preparation or the use of interfering medication. The clonidine test serves to distinguish true-positive from false-positive elevations of plasma normetanephrine. This test has an excellent diagnostic specificity (100%) and sensitivity (97%), although it has not yet been validated in more prospective studies (1,20,22).

In addition to the use of metanephrines for the diagnosis of PPGLs, they may also serve as biomarkers for estimating

**Table 63.2** Major medications that may cause falsely elevated test results for plasma and urinary metanephrines

|                                        | Plasma |    | Urine |    |
|----------------------------------------|--------|----|-------|----|
|                                        | NMN    | MN | NMN   | MN |
| Acetaminophen <sup>a</sup>             | ++     | –  | ++    | –  |
| Labetalol <sup>a</sup>                 | –      | –  | ++    | ++ |
| Sotalol <sup>a</sup>                   | –      | –  | ++    | ++ |
| α-Methyl dopa <sup>a</sup>             | ++     | –  | ++    | –  |
| Tricyclic antidepressants <sup>b</sup> | ++     | –  | ++    | –  |
| Buspirone <sup>a</sup>                 | –      | ++ | –     | ++ |
| Phenoxybenzamine <sup>b</sup>          | ++     | –  | ++    | –  |
| MAO inhibitors <sup>b</sup>            | ++     | ++ | ++    | ++ |
| Sympathomimetics <sup>b</sup>          | +      | +  | +     | +  |
| Cocaine <sup>b</sup>                   | ++     | +  | ++    | +  |
| Sulphasalazine <sup>a</sup>            | ++     | –  | ++    | –  |
| Levodopa <sup>c</sup>                  | +      | +  | ++    | +  |

Source: From Lenders JW et al. *J Clin Endocrinol Metab* 2014; 99(6): 1915–1942. With permission.

<sup>a</sup> Analytical interference for some but not all methods employing LC-ECD.

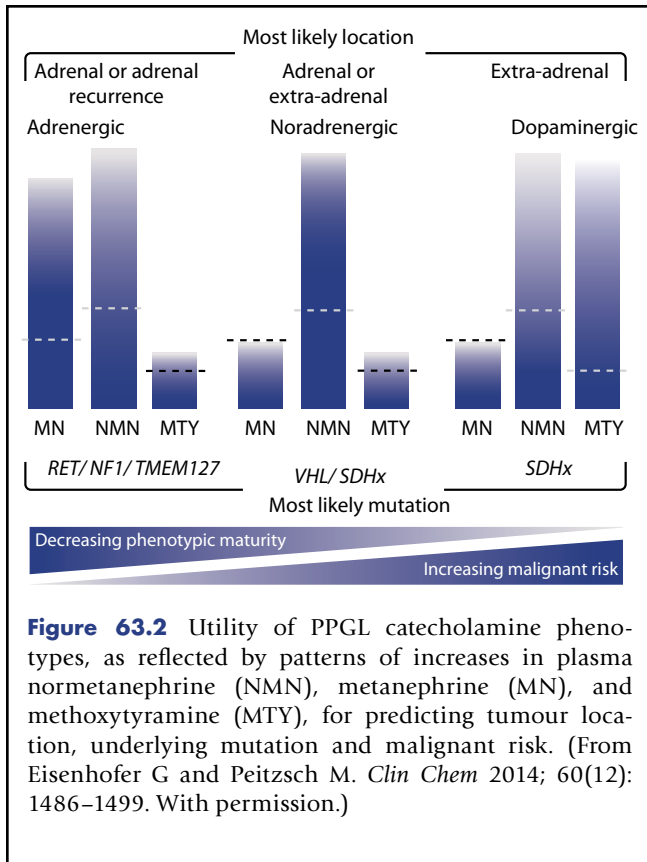
<sup>b</sup> Pharmacodynamic interference leading to increased levels affecting all analytical methods.

<sup>c</sup> Analytical interference with some LC-ECD assays, and also pharmacodynamic interference increase the dopamine metabolite 3-methoxytyramine affecting all analytical methods. Abbreviations: MAO, monoamine oxidase; MN, metanephrine; NMN, normetanephrine; ++, clear increase; +, mild increase; –, no increase.

tumour size and tumour location. A predominant metanephrine production usually indicates that the tumour is located in one or both adrenals, while significant metanephrine production is never the case in extra-adrenal chromaffin cell tumours (1,2,22). Some studies have suggested in the past that increases in urinary dopamine may predict metastatic disease. In recent years, however, it has become clear that increments in plasma MTY provide a much better predictor of the presence of metastatic PPGLs than urinary dopamine. For this reason, plasma MTY is regarded as a promising biomarker of metastatic PPGL and its measurement should be pondered in all patients at risk for metastatic PPGLs (7,20,22,25).

As documented by several studies, measuring metanephrines in plasma and urine can also be indicative of the kind of hereditary syndrome that may be associated with PPGLs. The underlying mutations are characterized by different biochemical profiles, and the biochemical results may therefore guide the priorities in genetic testing (Figure 63.2). This is elaborated further in the paragraph on genetic testing.

Tumours due to mutations in the *RET* (rearranged during transfection, a protooncogene associated with multiple endocrine neoplasia [MEN] type 2A) and *NF1* (neurofibromatosis type 1) genes show predominant increases in metanephrine. In contrast, tumours due to von Hippel–Lindau disease (VHL) and familial paraganglioma syndrome



(SDHx)-related tumours lack significant increases in metanephrine. Patients with a *VHL* mutation are characterized by solitary increases in normetanephrine, while additional increases in methoxytyramine characterize 70% of tumours due to mutations of *SDHD* and *SDHB* genes (1,20,22).

## IMAGING

After establishing a clear biochemical diagnosis, the next step is to localize the tumour. Several anatomical and functional imaging modalities are available for this purpose. Another important role of imaging is to detect multifocal tumours or metastatic lesions, since these may determine the choice of treatment (1,2). As 95% of all PPGLs are located in the abdomen or pelvis, imaging of these areas is the first consideration.

For the choice of the preferential anatomical imaging modality it has to be kept in mind that there are no large comparative studies on the performance of computed tomography (CT) versus MRI for the localization. The same holds true for the different functional imaging options.

CT is recommended as the first-choice anatomical modality because of its excellent spatial resolution (1,2). A modern CT scan has the ability to detect tumours of 5 mm and larger with a sensitivity for pheochromocytoma between 88–100%. Between 87–100% of PPGLs exhibit a mean attenuation of more than 10 Hounsfield units on unenhanced CT. Although calculation of the contrast washout using contrast-enhanced imaging may be helpful, the specificity of CT is limited and is therefore often followed by functional imaging, which has a higher

specificity. MRI is the anatomical imaging modality of first choice in patients with skull base and neck paragangliomas, in patients known to be allergic to CT contrast and in patients in whom radiation exposure should be limited, such as children, pregnant women and patients with a known mutation in one of the susceptibility genes (1,26,27).

Nuclear medicine scanning techniques include planar scintigraphy, single-photon emission CT (SPECT) and positron emission tomography (PET). The latter two methods can be used in a fusion mode with CT. These functional imaging modalities involve the use of radiotracers that target cellular receptors and transport channels for catecholamines, amino acids or glucose (28,29). Because of the radiation exposure, functional imaging cannot be used in pregnant women.

<sup>123</sup>I-MIBG scintigraphy is the functional imaging modality that has most widely been used to detect whether a tumour is a chromaffin cell tumour, whether there is a multifocal PPGL and whether there is metastatic disease. This test is indispensable to determine whether a patient qualifies for palliative <sup>131</sup>I-MIBG treatment.

Sensitivity of <sup>123</sup>I-MIBG ranges between 85–88% for pheochromocytoma and between 56–75% for paragangliomas, whereas specificity ranges from 70–100% to 84–100%, respectively. Sensitivity for metastatic PPGLs is between 56–83%, whereas for recurrent PPGLs it is approximately 75% (1,28,29).

It should be remembered that 50% of normal adrenal glands demonstrate physiological uptake of <sup>123</sup>I-MIBG, posing a risk of false-positive results (1,30,31). False-negative test results may be due to many drugs that may interfere with MIBG uptake, such as calcium channel blockers and tricyclic antidepressants. For a detailed list of these drugs the reader is referred to a paper from Solanki et al. (32).

A widely used ligand for PET scanning is 2-(<sup>18</sup>F)-fluoro-2-deoxy-D-glucose (<sup>18</sup>F-FDG), and in combination with CT this scan is particularly useful to detect metastatic disease. The reported sensitivities vary from 74–100%. Novel available PET tracers have been proven to be very useful for highly specific imaging of PPGLs such as 6-(<sup>18</sup>F)-fluoro-L-3,4-dihydroxyphenylalanine (<sup>18</sup>F-DOPA). Other ligands targeting somatostatin receptors, such as <sup>111</sup>In-DTP-pentetreotide, are available for SPECT, while the newer <sup>68</sup>Ga-DOTA-peptides (such as DOTATATE, DOTATOC, DOTANOC) can be used for PET/CT (1,28,29).

## GENETIC TESTING

Until now, 16 different PPGL susceptibility genes have been reported to cause PPGLs by germline mutations, including NF1 (neurofibromatosis type 1), RET (rearranged during transfection, protooncogene associated with MEN type 2), VHL, SDHD/SDHC/SDHB/SDHAF2/SDHA (familial paraganglioma syndromes), TMEM 127 (transmembrane protein 127), MAX (myc-associated factor X), HIF2alpha (hypoxia inducible factor) and others (FH [fumarate hydratase], MDH2 [malate dehydrogenase 2], EGLN1 and EGLN2 [Egl-9 family hypoxia inducible factor 1 and 2], and KIF1Bβ [kinesin family member B]).

The progress in genetic studies has led to the identification and characterization of distinct PPGL syndromes with evolving genotype-phenotype correlations (Table 63.3).

**Table 63.3** Genes and diseases

| Disease (phenotype MIM numbers)                                    | Genes       | Mutation rate (%) <sup>a</sup> | Main features                                                                                                                                                                                                      |
|--------------------------------------------------------------------|-------------|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Neurofibromatosis type 1 (162200)                                  | NF1         | 3                              | Café-au-lait spots, neurofibromas, axillary and inguinal freckling, Lisch nodules, osseous lesions, optic gliomas, mainly pheochromocytomas                                                                        |
| Multiple endocrine neoplasia type 2 (171400; 162300)               | RET         | 6                              | 2A: Medullary thyroid cancer, primary hyperparathyroidism, PPGL<br>2B: Medullary thyroid cancer, PPGL, Marfanoid habitus, mucocutaneous neuromas, gastrointestinal ganglioneuromatosis                             |
| von Hippel–Lindau disease (193300)                                 | VHL         | 7                              | Central nervous system or retinal hemangioblastomas, renal cell carcinoma, PPGL pancreatic neuroendocrine tumours and cysts, endolymphatic sac tumours, papillary cystadenoma of the epididymis and broad ligament |
| Hereditary paragangliomas (168000; 605373; 115310; 601650; 614165) | SDHx genes: |                                |                                                                                                                                                                                                                    |
|                                                                    | SDHB        | 10                             | PPGL, rare renal cancers, GIST                                                                                                                                                                                     |
|                                                                    | SDHD        | 9                              | PPGL, rare renal cancers, GIST                                                                                                                                                                                     |
|                                                                    | SDHC        | 1                              | PPGL, rare renal cancers, GIST                                                                                                                                                                                     |
|                                                                    | SDHA        | <1                             | PPGL, GIST                                                                                                                                                                                                         |
|                                                                    | SDHAF2      | <0.1                           | Head and neck paraganglioma                                                                                                                                                                                        |
| Familial pheochromocytomas (173300; 613403; 154950)                | TMEM127     | 1                              | Mainly pheochromocytomas, rare renal cancers mainly PPGL                                                                                                                                                           |
|                                                                    | MAX         | 1                              |                                                                                                                                                                                                                    |
| Polycythemia paraganglioma syndrome (603349)                       | EPAS1       | 1                              | Polycythaemia, PPGL, somatostatinoma                                                                                                                                                                               |
| Leiomyomatosis and renal cell cancer (150800)                      | FH          | 1                              | Cutaneous and uterine leiomyomas, type 2 papillary renal carcinoma, rare PPGL                                                                                                                                      |

Source: From Favier J et al. *Nat Rev Endocrinol* 2015; 11(2): 101–111. With permission.

Abbreviations: GIST, gastric stromal tumours; MIM, Mendelian inheritance in man; PPGL, paraganglioma and/or pheochromocytoma.

<sup>a</sup> The mutation rate is the percentage of patients with PPGL with mutations in the gene concerned.

Currently, patients with PPGL should undergo genetic testing for several reasons:

- Genetic testing identifies individuals at high risk for developing new or recurrent PPGL
- Genetic evaluation may indicate a high risk for malignancy since mutations in *SDHB* lead to metastatic disease in 40% or more of the affected patients
- There are significant implications of genetic testing for the patient's family members (33–39)

The development of next-generation sequencing (NGS) technology for sequencing of panels of multiple genes for PPGL syndromes presents a rapid, sensitive and cost-effective testing approach for PPGL patients. All tests for PPGL genetic testing should be performed by accredited laboratories. Informed consent must be obtained, and all family members should be offered genetic counselling (1,29,35,36,40).

In clinical practice, all patients who present with PPGL should be examined for features of one of the familial syndromes, some of which can be detected on physical examination (Table 63.3). These may include retinal angiomas in VHL syndrome, a thyroid mass in MEN2, café-au-lait spots in neurofibromatosis type 1 and a neck mass in paraganglioma syndromes. However, many patients with PPGLs do not present such features (7,34).

## PERIOPERATIVE MANAGEMENT

Adequate preparation prior to surgical resection of the PPGL is of paramount relevance since a hypertensive crisis and cardiovascular complications resulting from poor preoperative preparation may be life-threatening during anaesthesia and intraoperative tumour manipulation (5,8,41). Improved perioperative management of patients with PPGLs, including modern anaesthetic management, has resulted in reported survival rates of 98–100% in recent years. Proper preoperative blood pressure control should be achieved in all patients with hormonally functional PPGL (1,5,7,41–48). Such preoperative treatment regimen should be individualized and evaluated by a multidisciplinary team, taking into consideration comorbidities. Even in cases of optimal management, complete prevention of some hemodynamic instability cannot be achieved in all patients (45).

Preoperative alpha-blockade has been advocated for 7 up to 14 days to minimise intraoperative hypertension by preventing catecholamine-induced alpha-adrenoreceptor-mediated vasoconstriction. The medication should be started at a minimum dose (2 dd 10 mg) with slow up-titration to get the optimal therapeutic response (1,3,5) (Table 63.4). Traditionally, the irreversible, noncompetitive alpha-adrenoceptor blocker phenoxybenzamine has been used, but nowadays competitive alpha-blockers such

**Table 63.4** Presurgical medical preparation

| Drug                       | Starting time                          | Starting dose | Final dose <sup>a</sup> |
|----------------------------|----------------------------------------|---------------|-------------------------|
| Preparation 1              |                                        |               |                         |
| Phenoxybenzamine           | 10–14 d before surgery                 | 10 mg b.i.d.  | 1 mg/kg/d               |
| or Doxazosine              | 10–14 d before surgery                 | 2 mg/d        | 32 mg/d                 |
| Preparation 2              |                                        |               |                         |
| Nifedipine <sup>b</sup>    | As add-on to preparation 1 when needed | 30 mg/d       | 60 mg/d                 |
| or Amlodipine <sup>b</sup> | As add-on to preparation 1 when needed | 5 mg/d        | 10 mg/d                 |
| Preparation 3              |                                        |               |                         |
| Propranolol                | After at least 3–4 d of preparation 1  | 20 mg t.i.d.  | 40 mg t.i.d.            |
| or Atenolol                | After at least 3–4 d of preparation 1  | 25 mg/d       | 50 mg/d                 |

Source: From Lenders JW et al. *J Clin Endocrinol Metab* 2014; 99(6): 1915–1942. With permission.

Abbreviations: b.i.d., twice daily; t.i.d., three times daily.

<sup>a</sup> Higher doses usually unnecessary.

<sup>b</sup> Add when blood pressure cannot be controlled by  $\alpha$ -adrenoceptor blockade (preparation 1).

as doxazosin are also used as alternatives. On the basis of current evidence, there is no superior alpha-adrenoceptor blocker for the pretreatment of patients with PPGLs. Perioperative hemodynamics seem to be slightly better controlled with phenoxybenzamine, at the cost of more pronounced postoperative hypotension. However, side effects occurred less often in the group receiving doxazosin (46). Evidence from randomized controlled clinical studies regarding the comparable effectiveness of noncompetitive versus competitive adrenergic receptor blockers is unavailable at this time.

Of note, some authors argue that the effect of alpha-adrenoceptor blockade on perioperative complications has never been tested in a randomized trial. The recent observational study of Groeben et al. evaluated intraoperative hemodynamic conditions and the incidence of complications in patients with and without alpha-adrenoceptor blockade undergoing surgery for PPGLs. Only a slight difference in mean maximal systolic arterial pressure was detected between two groups, and no major complications occurred. As this was not a prospective randomized controlled trial, these results should be interpreted with caution and therefore the recommendation of preoperative preparation of PPGL patients with alpha-adrenoceptor blockade is still justified (49).

Addition of calcium channel blockers may help in further reduction of blood pressure and have been used effectively and safely as an adjunct to alpha-adrenoceptor blockade. Monotherapy with calcium channel blockers is

not recommended but may be an alternative in patients having severe orthostatic hypertension on alpha-adrenoceptor blocker treatment (50).

Beta-adrenoceptor blockade is indicated to control sinus tachycardia and other catecholamine-induced tachyarrhythmias, but only after several days of alpha-adrenoceptor blockade. If used alone, beta-adrenoceptor blockers may exacerbate hypertension by leaving alpha-adrenoceptor-mediated vasoconstriction unopposed.

Some centres use alpha-methyl-paratyrosine (metyrosine), a drug blocking the rate-limiting step of catecholamine synthesis in combination with alpha-adrenoceptor blockers for the short period before the surgery to further stabilize blood pressure. However, its use is limited by side effects, most commonly sedation, which occurs in the majority of patients (51). There are no randomized controlled trials that support the use of this drug.

Preoperative management should also include a high-sodium diet and fluid intake to reverse catecholamine-induced blood volume contraction and to prevent severe hypotension after tumour removal (1,3,5). In some centres, this is converted to infusion of saline (1–2 L) several days before the surgery. Caution is needed in patients with subclinical heart or renal failure (7,47).

Scientific data regarding perioperative medical management of normotensive PPGL patients are scant, and observational studies showed no clear benefit of preoperative alpha-adrenoceptor blockade in this group of patients. Nevertheless, patients with normotensive but hormonally active PPGLs should receive alpha-adrenoceptor blockade or calcium channel blockers because of potential dangers during surgery if this is omitted (1).

There is no consensus from randomized, controlled studies on the optimal target blood pressure. It has been advised to achieve a target blood pressure of less than 130/80 mmHg while seated and higher than 90 mmHg systolic while standing (with a heart rate of 60–70 bpm seated and 70–80 bpm standing). These targets should be individualized according to age and coexisting cardiovascular disease (1,43–48,50).

## SURGERY

Surgery of PPGLs is a high-risk procedure, but in experienced centres mortality is less than 2%. Whereas overall surgical morbidity for nonmetastatic PPGL in experienced hands is low, removal of large and locally invasive tumours and of head and neck paragangliomas may carry a considerable risk for surgical complications (7).

Although an individualized strategy based on patient characteristics (tumour location and size, multifocality, genetic background) and surgeon's preference is generally the best approach, there are high-quality data to show that for removal of a pheochromocytoma a minimally invasive adrenalectomy should be the standard of care. There are some exceptions for which open adrenalectomy is preferred to ensure complete tumour resection and to avoid local recurrence (1), such as large tumours (size >6 cm) and tumours that invade local organs (1,7,42,52–55).

Adrenal cortex-sparing procedures (subtotal adrenalectomy) have been advocated for patients with bilateral pheochromocytomas in the setting of hereditary syndromes such as VHL or MEN2. The main advantage of



subtotal compared to total adrenalectomy is the preservation of residual adrenocortical function (1,52,56). The typical indication in such context is the patient who had prior unilateral adrenalectomy and who has a small contralateral tumour (1,56,57). For preservation of adrenocortical function, a minimum of at least one-third of the adrenal gland has to be preserved. After minimal invasive adrenalectomy, about 80% of patients can be managed without hormonal substitution.

After surgery, patients require close monitoring in the intensive care unit for the first 24 hours. Hypotension and hypoglycaemia are the two main potential postoperative complications. In the majority of patients, the most likely cause of hypotension is the prolonged alpha-adrenoceptor blockade in the presence of low plasma catecholamine levels. Hypotension also can be caused by transient adrenocortical insufficiency, especially in patients after partial adrenalectomy who had contralateral adrenalectomy in the past (1). Hypotension should be treated with intravenous fluids, and if needed, vasopressor agents (1,47,52,58).

Blood glucose levels should be carefully monitored for timely detection of hypoglycaemia, resulting from decreased glucose production and increased glucose utilization due to a decrease in catecholamines and persistent effect of alpha-adrenoceptor blockade. In addition, beta-adrenoceptor blockade contributes to an impaired recovery from hypoglycaemia (1,42).

After surgery, blood pressure is often normalized by the time of hospital discharge, and plasma catecholamines slowly return to normal levels within a few days (1,42,52). If hypertension persists, a residual tumour mass after incomplete resection has to be considered. However even if tumour resection has been complete, up to 25% of patients may remain hypertensive in the long term due to vascular remodelling and associated target-organ damage or to pre-existing primary hypertension.

Early postoperative follow-up is recommended and blood pressure and plasma or urinary metanephrines should be measured 1–2 weeks after the surgery. If plasma metanephrines are completely normalized after surgery, resection is considered complete. Elevated levels may indicate the presence of residual tumour, a second PPGL or metastases (1,42,52).

## LONG-TERM FOLLOW-UP

After successful resection of a PPGL, patients should undergo long-term follow-up to detect recurrent tumours, new tumours or metastatic disease. The lifetime risk of recurrence varies by genotype (42,54,59) (Table 63.5).

The European Society of Endocrinology Clinical Practice Guideline proposed a standardized long-term follow-up in all patients operated for PPGLs (54). The key recommendations for the duration of follow-up and monitoring methods are as follows (54):

- Annual follow-up is suggested for at least 10 years in all patients operated on for a PPGL, while high-risk patients (young age, with a genetic disease, with a large tumour, with a paraganglioma) should be offered lifelong annual follow-up.
- Measurement of plasma or urinary metanephrines and MTY every year to screen for local or metastatic recurrences or new tumours.

**Table 63.5** Risk of new event and number of patients needed to screen (NNS) to detect one new event during the first 5 years following surgery

| Group/Subgroup                        | Risk of new event % (95% CI) | NNS n (95% CI) |
|---------------------------------------|------------------------------|----------------|
| Overall                               | 10 (8, 14)                   | 10 (7, 13)     |
| Tumour location                       |                              |                |
| Pheochromocytoma                      | 8 (6, 11)                    | 12 (9, 18)     |
| Thoraco-abdomino-pelvic paraganglioma | 18 (11, 31)                  | 5 (3, 9)       |
| Head and neck paraganglioma           | 25 (11, 57)                  | 4 (2, 9)       |
| Age at surgery                        |                              |                |
| ≥20 years old at surgery              | 9 (7, 12)                    | 11 (8, 15)     |
| <20 years old at surgery              | 27 (15, 51)                  | 4 (2, 7)       |
| Phenotypic and genetic status         |                              |                |
| Non-syndromic/genetic disease         | 7 (5, 11)                    | 13 (9, 21)     |
| Syndromic/genetic disease             | 17 (12, 24)                  | 6 (4, 9)       |
| Tumour size                           |                              |                |
| Tumour <150 mm                        | 10 (7, 14)                   | 10 (7, 14)     |
| Tumour ≥150 mm                        | 26 (6, 100)                  | 4 (1, 15)      |

Source: From Plouin PF et al. *Eur J Endocrinol* 2016; 174(5): G1–G10. With permission.

- Perform imaging tests every 1–2 years in patients with a biochemically inactive PPGL.

## REFERENCES

- Lenders JW, Duh QY, Eisenhofer G et al. Pheochromocytoma and paraganglioma: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2014; 99: 1915–1942.
- Eisenhofer G, Peitzsch M. Laboratory evaluation of pheochromocytoma and paraganglioma. *Clin Chem* 2014; 60: 1486–1499.
- Young JWF, Calhoun DA, Lenders JWM et al. Screening for endocrine hypertension: An endocrine society scientific statement. *Endocr Rev* 2017; 38: 103–122.
- Reisch N, Peczkowska M, Januszewicz A, Neumann HP. Pheochromocytoma: Presentation, diagnosis and treatment. *J Hypertens* 2006; 24: 2331–2339.
- Darr R, Lenders JW, Hofbauer LC et al. Pheochromocytoma – Update on disease management. *Ther Adv Endocrinol Metab* 2012; 3: 11–26.
- Sinclair AM, Isles CG, Brown I et al. Secondary hypertension in a blood pressure clinic. *Arch Intern Med* 1987; 147: 1289–1293.
- Kaplan NM, Victor RG. *Kaplan's Clinical Hypertension*. Wolters Kluwer: Philadelphia, 2015.
- Prejbisz A, Lenders JW, Eisenhofer G, Januszewicz A. Cardiovascular manifestations of pheochromocytoma. *J Hypertens* 2011; 29: 2049–2060.
- Platts JK, Drew PJ, Harvey JN. Death from pheochromocytoma: Lessons from a post-mortem survey. *J R Coll Physicians Lond* 1995; 29: 299–306.
- Berends AMA, Buitenwerf E, de Krijger RR et al. Incidence of pheochromocytoma and sympathetic paraganglioma in the Netherlands: A nationwide study and systematic review. *Eur J Intern Med* May 2018; 51: 68–73.



11. Pamporaki C, Hamplova B, Peitzsch M et al. Characteristics of pediatric vs adult pheochromocytomas and paragangliomas. *J Clin Endocrinol Metab* 2017; 102: 1122–1132.
12. Manger WM, Gifford RW Jr. *Clinical and Experimental Pheochromocytoma*. 2nd ed. Blackwell Science: Malden, MA; 1996.
13. Tolis G, Kuchel O. The multiple faces of the pheochromocytoma. *CMAJ* 1977; 116: 337–338.
14. Zelinka T, Petrak O, Turkova H et al. High incidence of cardiovascular complications in pheochromocytoma. *Horm Metab Res* 2012; 44: 379–384.
15. Stolk RF, Bakx C, Mulder J et al. Is the excess cardiovascular morbidity in pheochromocytoma related to blood pressure or to catecholamines? *J Clin Endocrinol Metab* 2013; 98: 1100–1106.
16. Prejbisz A, Lenders JW, Eisenhofer G, Januszewicz A. Mortality associated with pheochromocytoma. *Horm Metab Res* 2013; 45: 154–158.
17. Giavarini A, Chedid A, Bobrie G et al. Acute catecholamine cardiomyopathy in patients with pheochromocytoma or functional paraganglioma. *Heart* 2013; 99: 1438–1444.
18. Agarwal V, Kant G, Hans N, Messerli FH. Takotsubo-like cardiomyopathy in pheochromocytoma. *Int J Cardiol* 2011; 153: 241–248.
19. Eisenhofer G, Rivers G, Rosas AL et al. Adverse drug reactions in patients with pheochromocytoma: Incidence, prevention and management. *Drug Saf* 2007; 30: 1031–1062.
20. Eisenhofer G, Tischler AS, de Krijger RR. Diagnostic tests and biomarkers for pheochromocytoma and extra-adrenal paraganglioma: From routine laboratory methods to disease stratification. *Endocr Pathol* 2012; 23: 4–14.
21. Fassnacht M, Arlt W, Bancos I et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. *Eur J Endocrinol* 2016; 175: G1–G34.
22. van Berkel A, Lenders JW, Timmers HJ. Diagnosis of endocrine disease: Biochemical diagnosis of pheochromocytoma and paraganglioma. *Eur J Endocrinol* 2014; 170: R109–R119.
23. Rao D, Peitzsch M, Prejbisz A et al. Plasma methoxytyramine: Clinical utility with metanephrines for diagnosis of pheochromocytoma and paraganglioma. *Eur J Endocrinol* 2017; 177: 103–113.
24. Eisenhofer G, Lenders JW, Siegert G et al. Plasma methoxytyramine: A novel biomarker of metastatic pheochromocytoma and paraganglioma in relation to established risk factors of tumour size, location and SDHB mutation status. *Eur J Cancer* 2012; 48: 1739–1749.
25. Baudin E, Habra MA, Deschamps F et al. Therapy of endocrine disease: Treatment of malignant pheochromocytoma and paraganglioma. *Eur J Endocrinol* 2014; 171: R111–R122.
26. Maurea S, Cuocolo A, Reynolds JC et al. Diagnostic imaging in patients with paragangliomas. Computed tomography, magnetic resonance and MIBG scintigraphy comparison. *Q J Nucl Med* 1996; 40: 365–371.
27. Sahdev A, Sohaib A, Monson JP et al. CT and MR imaging of unusual locations of extra-adrenal paragangliomas (pheochromocytomas). *Eur Radiol* 2005; 15: 85–92.
28. Timmers HJ, Taieb D, Pacak K. Current and future anatomical and functional imaging approaches to pheochromocytoma and paraganglioma. *Horm Metab Res* 2012; 44: 367–372.
29. Brito JP, Asi N, Gionfriddo MR et al. The incremental benefit of functional imaging in pheochromocytoma/paraganglioma: A systematic review. *Endocrine* 2015 Sep; 50(1): 176–186.
30. Nakatani T, Hayama T, Uchida J et al. Diagnostic localization of extra-adrenal pheochromocytoma: Comparison of (123)I-MIBG imaging and (131)I-MIBG imaging. *Oncol Rep* 2002; 9: 1225–1227.
31. Lev I, Kelekar G, Waxman A, Yu R. Clinical use and utility of metaiodobenzylguanidine scintigraphy in pheochromocytoma diagnosis. *Endocr Pract* 2010; 16: 398–407.
32. Solanki KK, Bomanji J, Moyes J et al. A pharmacological guide to medicines which interfere with the biodistribution of radiolabelled meta-iodobenzylguanidine (MIBG). *Nucl Med Commun* 1992; 13: 513–521.
33. Rana HQ, Rainville IR, Vaidya A. Genetic testing in the clinical care of patients with pheochromocytoma and paraganglioma. *Curr Opin Endocrinol Diabetes Obes* 2014; 21: 166–176.
34. Brito JP, Asi N, Bancos I et al. Testing for germline mutations in sporadic pheochromocytoma/paraganglioma: A systematic review. *Clin Endocrinol (Oxf)* 2015; 82: 338–345.
35. Welander J, Andreasson A, Juhlin CC et al. Rare germline mutations identified by targeted next-generation sequencing of susceptibility genes in pheochromocytoma and paraganglioma. *J Clin Endocrinol Metab* 2014; 99: E1352–E1360.
36. Kantorovich V, King KS, Pacak K. SDH-related pheochromocytoma and paraganglioma. *Best Pract Res Clin Endocrinol Metab* 2010; 24: 415–424.
37. Amar L, Bertherat J, Baudin E et al. Genetic testing in pheochromocytoma or functional paraganglioma. *J Clin Oncol* 2005; 23: 8812–8818.
38. Erlic Z, Rybicki L, Peczkowska M et al. Clinical predictors and algorithm for the genetic diagnosis of pheochromocytoma patients. *Clin Cancer Res* 2009; 15: 6378–6385.
39. Mannelli M, Castellano M, Schiavi F et al. Clinically guided genetic screening in a large cohort of Italian patients with pheochromocytomas and/or functional or nonfunctional paragangliomas. *J Clin Endocrinol Metab* 2009; 94: 1541–1547.
40. Davidson DF. Pheochromocytoma with normal urinary catecholamines: The potential value of urinary free metadrenalines. *Ann Clin Biochem* 2002; 39: 557–566.
41. Moraitis AG, Martucci VL, Pacak K. Genetics, diagnosis, and management of medullary thyroid carcinoma and pheochromocytoma/paraganglioma. *Endocr Pract* 2014; 20: 176–187.
42. Mannelli M, Dralle H, Lenders JW. Perioperative management of pheochromocytoma/paraganglioma: Is there a state of the art? *Horm Metab Res* 2012; 44: 373–378.
43. Lafont M, Fagour C, Haissaguerre M et al. Per-operative hemodynamic instability in normotensive patients with incidentally discovered pheochromocytomas. *J Clin Endocrinol Metab* 2015; 100: 417–421.
44. Isaacs M, Lee P. Preoperative alpha-blockade in pheochromocytoma and paraganglioma: Is it always necessary? *Clin Endocrinol (Oxf)* 2017; 86: 309–314.
45. Kocak S, Aydinoglu S, Canakci N. Alpha blockade in preoperative preparation of patients with pheochromocytomas. *Int Surg* 2002; 87: 191–194.
46. van der Zee PA, de Boer A. Pheochromocytoma: A review on preoperative treatment with phenoxybenzamine or doxazosin. *Neth J Med* 2014; 72: 190–201.
47. Pacak K. Preoperative management of the pheochromocytoma patient. *J Clin Endocrinol Metab* 2007; 92: 4069–4079.
48. Braeckel P V, Carlier S, Steelant PJ et al. Perioperative management of pheochromocytoma. *Acta Anaesthesiol Belg* 2009; 60: 55–66.
49. Groeben H, Nottebaum BJ, Alesina PF et al. Perioperative alpha-receptor blockade in pheochromocytoma surgery: An observational case series. *Br J Anaesth* 2017; 118: 182–189.
50. Lebuffe G, Dosseh ED, Tek G et al. The effect of calcium channel blockers on outcome following the surgical treatment of pheochromocytomas and paragangliomas. *Anaesthesia* 2005; 60: 439–444.
51. Steinsapir J, Carr AA, Prisant LM, Bransome ED, Jr. Metyrosine and pheochromocytoma. *Arch Intern Med* 1997; 157: 901–906.
52. Walz MK, Alesina PF, Wenger FA et al. Laparoscopic and retroperitoneoscopic treatment of pheochromocytomas and retroperitoneal paragangliomas: Results of 161 tumors in 126 patients. *World J Surg* 2006; 30: 899–908.
53. Grubbs EG, Rich TA, Ng C et al. Long-term outcomes of surgical treatment for hereditary pheochromocytoma. *J Am Coll Surg* 2013; 216: 280–289.
54. Plouin PF, Amar L, Dekkers OM et al. European Society of Endocrinology Clinical Practice Guideline for long-term follow-up of patients operated on for a pheochromocytoma or a paraganglioma. *Eur J Endocrinol* 2016; 174: G1–G10.
55. Plouin PF, Duclos JM, Soppelsa F et al. Factors associated with perioperative morbidity and mortality in patients with pheochromocytoma: Analysis of 165 operations at a single center. *J Clin Endocrinol Metab* 2001; 86: 1480–1486.
56. Kaye DR, Storey BB, Pacak K et al. Partial adrenalectomy: Underused first line therapy for small adrenal tumors. *J Urol* 2010; 184: 18–25.
57. Alesina PF, Hinrichs J, Meier B et al. Minimally invasive corticosparring surgery for bilateral pheochromocytomas. *Langenbecks Arch Surg* 2012; 397: 233–238.
58. Caoili EM, Korobkin M, Francis IR et al. Adrenal masses: Characterization with combined unenhanced and delayed enhanced CT. *Radiology* 2002; 222: 629–633.
59. Amar L, Fassnacht M, Gimenez-Roqueplo AP et al. Long-term post-operative follow-up in patients with apparently benign pheochromocytoma and paraganglioma. *Horm Metab Res* 2012; 44: 385–389.



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# Section X

## Additional Aspects

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# FOLLOW-UP OF THE HYPERTENSIVE PATIENT

# 64

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## INTRODUCTION

Hypertension is a chronic, lifelong and progressive condition with potential detrimental effects on the cardiovascular system. Follow-up of hypertensive patients is therefore a key element of clinical management, essential for education and lifestyle modification, control of blood pressure (BP), fine-tuning of therapy, recognition of adverse effects of antihypertensive drugs and timely identification of target-organ damage.

Robust data on long-term management are, however, scarce and fragmented. The limited availability of relevant information is reflected in contemporary guidelines for the management of hypertension where diagnostic workup and therapy feature prominently compared to less specific guidance on follow-up strategies. Follow-up strategies were briefly mentioned in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) but are almost completely absent in the JNC 8 guidelines (1,2). In contrast, the 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines contain a specific section on follow-up (3); the recommendations are, however, based on expert opinion, common sense and clinical experience, and only to limited extent on evidence. The recently published 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines provide specific recommendations about visit frequency in patients taking antihypertensive therapy (4). It is recommended that 'adults initiating a new or adjusted drug regimen for hypertension should have a follow-up evaluation of adherence and response to treatment at monthly intervals until control is achieved'. This recommendation is mainly based on two large clinical trials (Action to Control Cardiovascular Risk in Diabetes [ACCORD] and Systolic Blood Pressure Intervention Trial [SPRINT]) (5,6), and it remains to be determined whether this clinical trial-derived protocol can be applied to 'real life' clinical practice.

From a clinical perspective, there are three key questions regarding long-term management of patients with hypertension:

1. *When?* How often should the follow-up visits take place?
2. *Who?* Who should conduct the follow-up visits?
3. *What?* What are the main tasks during the follow-up visits?

The aims of this chapter are to summarise the relevant clinical aspects of follow-up visits, to review the data available on this topic and to provide suggestions for future research directions in this field.

## WHEN: HOW OFTEN?

When should I see this patient again? Does the visit interval affect blood pressure control and subsequently cardiovascular events?

There are no generally applicable evidence-based answers to these common questions, even though they directly relate to the use of medical and healthcare resources and outcomes in hypertensive patients.

The frequency of follow-up visits depends mainly on two factors: the level of BP control and the severity of hypertension and associated organ damage. It appears reasonable to assume that patients with hypertensive urgencies require close follow-up after discharge from hospital. A randomised controlled study in 144 emergency room patients with diastolic BP  $\geq 100$  mmHg, however, failed to prove that increased follow-up frequency significantly improved BP control (7). In contrast, patients with high normal blood pressure or mild hypertension and low cardiovascular risk might not need very frequent follow-up. According to the 2013 ESH/ESC guidelines, 'Individuals with high normal blood pressure or white-coat hypertension ... even if untreated, ... should be scheduled for regular follow-up (at least annual visits)' (3). In patients with comorbidities, however, more frequent follow-up may be required. In a study of more than 6000 hypertensive patients treated by primary care physicians in Canada, it



was found that the annual number of return visits was more than twofold higher in patients with three or more comorbidities compared to those without other conditions (8). However, exactly why more frequent visits are required and whether they translate into better long-term outcomes remains unclear.

## UNCONTROLLED BLOOD PRESSURE

Several observational studies and one randomised study have evaluated the impact of visit frequency on BP control in hypertensive patients with uncontrolled BP.

In a cohort of 429 hypertensive patients from two urban family practices, the average return visit interval for patients with uncontrolled BP patients was 71.2 days, while the corresponding interval for those with controlled BP patients was 84.1 days ( $p < 0.001$ ) (9). Of major clinical importance, decrease in systolic BP was significantly greater with shorter return visit intervals. Another large retrospective study analysed the data of more than 5000 hypertensive patients with type 2 diabetes treated by primary care physicians (10). BP control was achieved after a median of 1.5 months in patients with visit intervals of less than 1 month, while a median of 12.2 months was needed in patients with visit intervals of more than 1 month ( $p < 0.0001$ ). A large retrospective study evaluated a cohort of more than 25,000 patients with type 2 diabetes treated for 9 years by primary care physicians (11). BP control ( $<130/85$  mmHg) was achieved after a median of 1.3 months in patients visiting their physician more frequently (1–2 weeks) compared to 13.9 months in those with less frequent (3–6 months) visits ( $p < 0.001$ ). In multivariate analysis, doubling time between visits was associated with an 87% increase in median time to achieve BP control. A retrospective study of almost 100,000 participants with newly diagnosed hypertension from the Kaiser Permanente Insurance System in California found that mean follow-up was significantly longer in patients with uncontrolled compared with patients with controlled BP (292.9 vs. 232.2 days) (12). The average number of visits was higher in the controlled compared with the uncontrolled group (4.1 vs. 3.1 visits) and the likelihood of reaching BP control decreased with increasing intervals between visits. Indeed, visit intervals  $>180$  days were associated with the lowest likelihood of achieving BP control, while visit intervals  $<2$  weeks were associated with the highest likelihood of achieving target BP. Another retrospective study evaluated the association between visit frequency and time to BP control in almost 3000 patients younger than 40 years of age with incident hypertension treated in primary care – an important patient group who experience lower control rates compared with elderly patients (13). This study also showed that shorter visit intervals were associated with better BP control rates during a 2-year follow-up period. Interestingly, the corresponding rates of initiation of drug therapy were lower (21%) in the frequent visit group (compared to 29% in less-frequent visit groups).

The data above all derive from observational studies with inherent limitations. The only randomised controlled study comes from a small cohort of 156 hypertensive patients with uncontrolled BP treated by family physicians in Canada. This study compared frequent visits (every 2 weeks for 16 weeks) with usual care for a

12-month follow-up period (14) and patients in the intervention group had significantly lower office and ambulatory BP values.

## CONTROLLED BLOOD PRESSURE

Once BP control is achieved, less frequent follow-up visits are reasonable. A limited number of studies, however, provide evidence in this context.

A randomised clinical trial of 609 patients with controlled BP treated by family practitioners in Canada compared the equivalence of 3-month and 6-month follow-up visits in terms of BP control, patient satisfaction and adherence to therapy (15). During a follow-up period of 33.6 months, there were no significant differences between the two groups in mean BP, BP control rates, patient satisfaction or adherence to treatment, indicating that 6-month visit intervals might be appropriate for patients with controlled BP. It should be mentioned, however, in both treatment arms the actual between-visit time was much shorter than originally planned (2.16 months for the 6-month group and 1.89 months for the 3-month group), thereby challenging the conclusions that can be drawn from this study.

## EFFECT OF VISIT FREQUENCY ON CARDIOVASCULAR OUTCOMES

The aforementioned studies indicate that more frequent return visits translate into significant benefits in surrogate endpoints such as overall BP control rates and time to achieving BP control. However, they do not attest to whether these intermediate benefits are associated with long-term cardiovascular risk reduction.

A large population-based retrospective cohort study in 90,000 patients with hypertension treated in British primary care practices between 1986 and 2010 provides information about the impact of delays in follow-up visits on cardiovascular events and death (16). During a median follow-up period of 37.4 months, almost 10,000 participants suffered a nonfatal cardiovascular event or died. It was found that when time to follow-up visit exceeded 2.7 months, risk of cardiovascular events was increased by 18% ( $p < 0.001$ ). Likewise, a gradual risk increase was observed with delays in treatment intensification. Similar associations were observed when only the mortality risk was studied.

## CRITICAL EVALUATION

Overcoming clinical inertia through treatment intensification is probably a major factor for better BP control with greater frequency of visits. Other factors such as intensive lifestyle modification and better adherence to antihypertensive therapy appear to be equally important.

Prompt BP control has been associated with significant cardiovascular benefits in several studies. In the VALUE trial, rapid BP control (within 6 months) was associated with decreased rates of cardiovascular events, irrespective of treatment allocation (amlodipine or valsartan) (17). Likewise, in the open extension of the Systolic Hypertension in Europe (Syst-Eur) Trial, immediate BP control was

associated with reduced risk of cardiovascular events compared with delayed BP control (18). More recently, similar findings were observed in the ADVANCE-ON study, the open follow-up observation phase of the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial (19). On the other hand, a potentially significant barrier to increased visit frequency in real-life practice might be the increased demand for healthcare resources in primary care (20–22). Therefore, innovative ways of delivering healthcare should be explored where more frequent visits are required.

The opinions and beliefs of practicing physicians are of paramount importance for the implementation of guideline recommendations, particularly where guidelines are vague or not provided at all. In the context of follow-up of hypertensive patients, a few older studies shed light on this issue. A study of 50 general practitioners in South Glamorgan, Wales, assessed their opinions on visit frequency for patients with uncomplicated controlled hypertension (23). On average, doctors thought that hypertensive patients should be followed up every 14.8 weeks; however, a wide range of responses was observed, with visit frequency every 2 weeks to once a year. The main factors guiding these decisions were BP severity, age, and prior antihypertensive therapy. Another study evaluated visit frequency and its determinants among 457 patients in UK during a 14-year follow-up period (24). The mean and the median intervals between visits were 113 and 91 days, respectively. The between-visit interval was mainly affected by the severity of hypertension and the duration of follow-up. The background of primary care physicians might also play a role. In a study of 273 female physicians in Canada, it was found that community practice physicians scheduled more frequent follow-up visits than physicians with academic appointment (25).

A recent study simulated the impact of three intervention strategies on BP control using national survey data and validated the findings in two large clinical trials (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial [ALLHAT] and VALUE) (26). Enhanced treatment intensification had the greatest impact on BP control followed by increased visit frequency and increased adherence. When all three interventions were optimised, appropriate BP control was predicted to be achieved in 95% of hypertensive patients, highlighting the importance of follow-up frequency in hypertension treatment strategies.

Whilst all these data provide evidence of the importance of tailored follow-up strategies for BP control and cardiovascular outcome, specific guidance cannot be provided at this point in time. The overarching evidence that more frequent visits are associated with better outcomes should, however, be taken into account in the care of individual patients.

## WHO SHOULD FOLLOW UP ON PATIENTS WITH HYPERTENSION?

Should all patients with hypertension be followed up by primary and secondary care physicians? What is the role of allied healthcare professionals in long-term management? Will eHealth and mHealth have an impact on patient management?

Primary care physicians and hypertension specialists are facing increasing workloads worldwide. Innovative interventions that include other healthcare professionals such as pharmacists and nurses, the use of eHealth technologies such as mobile phones and other devices to monitor patients remotely, and the involvement of patients and their relatives through self-monitoring and home BP telemonitoring might not only reduce physicians' workload but also significantly improve BP control and cardiovascular outcomes. Team-based care has indeed been found to be associated with significantly greater reductions in BP and increased rates of BP control compared to usual care (27). We would like to focus on the roles of pharmacists and nurses in hypertension management.

## PHARMACISTS

Pharmacists are highly accessible in most parts of the world and often build long-term relationships with patients. Their role in hypertension management includes regular BP monitoring, patient education on lifestyle modification, advice on adherence to therapy and feedback to the treating physician. Of equal importance, pharmacists can also play an important role in a holistic approach to the prevention and treatment of cardiovascular diseases through improving control of other cardiovascular risk factors such as diabetes, dyslipidemia, smoking and obesity (28–31).

Several studies evaluated the impact of pharmacist involvement on adherence to antihypertensive therapy and BP control. A meta-analysis of 19 randomised controlled trials with more than 14,000 participants demonstrated greater BP reduction compared with usual care (32). Another recent meta-analysis pooled data from 63 studies evaluating the effects of pharmacist-led chronic disease management (33). In 15 studies, pharmacist-led compared with usual care was found to be associated with similar numbers of clinical events, similar health-related quality of life and similar number of hospitalisations, urgent care and visits to the emergency department. Mixed findings were observed for patient satisfaction, office visits and cost outcomes, while BP control was more likely to be achieved with pharmacist-led care. A recent randomised controlled study of 248 patients in Alberta, Canada, where pharmacists prescribe drugs, request laboratory tests after appropriate training and communicate prescription changes to the treating physician, showed that pharmacist intervention was associated with greater systolic BP reduction and increased probability of achieving BP control (34).

Appropriate education and training of pharmacists in accurate BP measurement and hypertension management are paramount for wide-range implementation of such strategies, and expanding the role of community pharmacists requires significant changes in the health network and legislation changes in many countries.

## NURSES

Nurses have traditionally been involved in the measurement of BP and provide advice on lifestyle modification and adherence to antihypertensive therapy. The closer and more relaxed relationship between nurses and patients

results in lower BP values obtained by nurses compared to physicians (35) and longer conversations focused on prevention (36). Nurses have been granted the authority to prescribe medicines, to be reimbursed for primary care services and to admit patients to hospital in several parts of the world. Generally, more evidence on the effectiveness of nurse-led services in terms of BP control and cardiovascular outcomes is required (37).

A large randomised controlled trial found no differences in patient outcomes between primary care physicians and nurse practitioners who had similar authorities and responsibilities (38). Other studies in community settings both in Europe and the US also failed to demonstrate significant benefits of nurse-led clinics (39–41). In contrast, several small studies have shown beneficial effects with nurse-led practices, attributed to stricter implementation of guideline recommendations and adherence to therapeutic protocols, and more regular follow-up visits. A meta-analysis of 33 studies reported that nurse-led interventions – through a stepped-treatment algorithm, nurse prescribing or community monitoring – were associated with greater systolic BP reductions compared to usual care. A sub-analysis of six studies in primary care also demonstrated that nurse-led clinics showed greater reduction of BP compared with usual care (42). The benefits of nurse-led clinics compared with physician-led care are even greater in diabetic patients with hypertension (43). The most recent meta-analysis pooled data from studies evaluating the effects of community-based nurse-led interventions in patients with chronic conditions (44). This analysis of 10 studies with almost 4000 participants revealed that compared with usual care, nurse-led interventions were associated with a trend towards lower BP. When nurses were specifically trained and studies were of adequate size (>200 participants), statistically significant BP reduction favouring nurse-led interventions was observed in patients with diabetes for systolic BP and in patients with cardiovascular disease for diastolic BP (44).

## DIGITAL INTERVENTION

Interactive digital interventions are internet-based packages delivered to the patient either by computer or by phone, which provide health information, focussing on behavioural modification and decision support, and allow remote monitoring by physicians. Self-management of hypertension guided by interactive digital intervention can lead to improved education and BP control in hypertensive patients (45).

A recent meta-analysis of seven randomised controlled trials pooled data from more than 1200 participants and revealed that interactive digital interventions were associated with significantly greater BP reduction compared with usual care (46). However, the benefits were not consistent among all studies, and it remains unclear whether BP reduction is sustained and whether it translates to cardiovascular risk reduction. In a meta-analysis of 51 studies, digital health interventions were found to be associated with significant reductions in cardiovascular risk and cardiovascular outcomes (47). A Cochrane meta-analysis of the impact of mobile phone messaging on facilitation of self-managing chronic disease identified only one randomised controlled study for the management of hypertension (48) – a small study evaluating the effect of text

messaging on BP during a 6-month follow-up period (49). No significant differences between participants with or without text messaging were found in systolic or diastolic BP or in BP control rates, while only a marginal benefit in compliance to therapy was observed with intervention. Clearly, the quality of studies in this field must be further improved in order to impact on clinical care.

## MOBILE APPLICATIONS

Smartphone devices have revolutionised modern communication and are used by the majority of adults worldwide, with constantly increasing numbers of elderly users. Health-related smartphone applications represent a fast-growing field, rendering mobile health (mHealth) an attractive approach for the management of chronic diseases (50–52). mHealth applications are widely accepted, with more than half of smartphone owners using at least one mHealth application (53), including the assessment of heart rate, atrial fibrillation, physical activity, sleep quality and BP. Smartphone applications may be used in hypertension management through recording and storing BP values inserted manually, automatic transmission of measurements from the device to the smartphone, and more impressively, by turning the smartphone into a BP device permitting cuffless BP measurements (54). All applications, however, have several limitations, with the major drawback being the limited accuracy of cuffless measurements (55).

A recent statement of the American Heart Association on mHealth applications in cardiovascular disease included BP management among the potential aspects for intervention, favouring the applications but also highlighting the lack of standardisation (56). Recently, the ESH endorsed ESH CARE (57); this mobile application facilitates the collection and the transmission of BP measurements and information about drug therapy as well as feedback from physicians. Moreover, educational information is provided on hypertension and its cardiovascular complications. Another application has been developed for patients with suspected primary aldosteronism and has recently been endorsed by ESH (58).

## HOME BLOOD PRESSURE TELEMONITORING

Home BP monitoring is encouraged by most hypertension guidelines in order to ensure patient engagement and improve BP control. Home BP telemonitoring includes transmission of measurements to a healthcare provider through various remote methods.

Home BP telemonitoring compared with usual care has been found to be associated with increased frequency of treatment intensification (59). A systematic review in 2013 revealed that telemonitoring was associated with better BP control and improvements in the physical components of quality of life when compared to usual care (60). However, the healthcare costs per patient were approximately 600€ greater for those undergoing telemonitoring, and there was no consistent effect on treatment adherence (60). A more recent meta-analysis of 46 randomised studies with almost 14,000 participants found that home BP telemonitoring was associated with significant reductions in systolic and diastolic BP, along with improved control of hypertension (61). Home



BP telemonitoring with additional support compared with telemonitoring alone was associated with a trend towards reduced BP levels. Several patient characteristics have been identified as predictors of better outcomes with telemonitoring, including younger age, higher baseline diastolic BP, reduced salt intake, fewer antihypertensive drugs and absence of diabetes mellitus (62).

Despite evidence supporting the use of home BP telemonitoring in the management of arterial hypertension, this approach is not widely used in contemporary clinical practice. Potential barriers include uncertainties about data security and infrastructure limitations and the lack of simple, cost-effective and user-friendly systems that are required to gain wide acceptability by both healthcare professionals and patients. Moreover, financial incentives for healthcare professionals are needed in order to make telemonitoring attractive for physicians, pharmacists and nurses (63). Patients seem keen to use telemonitoring and find it easy to perform but question its utility and ask for enhanced feedback by physicians; lack of familiarity with technology, out-of-town jobs and hobbies are identified by patients as potential obstacles to implementation (64).

## VIRTUAL CLINICS

Involvement of allied health professionals and eHealth technologies has the potential to reduce face-to-face visits to primary care physicians or hypertension specialists. At the same time there may be increased demand for healthcare professionals to review ambulatory data and feedback to patients and other members of the healthcare team. These tasks will require dedicated and protected time, probably in the form of virtual clinics involving a multidisciplinary team where all available information is reviewed, and individualized diagnostic and therapeutic approaches are discussed. Without sufficient time allocated to management of data that are not directly acquired by the physician, these new approaches are bound to fail and possibly even to pose a risk to patients with hypertension.

## CRITICAL EVALUATION: LESSONS FROM THE UK AND THE US

Although physicians dominate hypertension care in most European countries, some healthcare systems explore alternative modes of hypertension care. A recent survey among 117 general practices in South West England sheds light on the organisation of hypertension care in the UK and its impact on BP control (65). Most practices (73%) changed their hypertension care arrangements, mainly through strengthened roles of healthcare assistants (19.4%), nurses and nurse-led clinics (16.7%) and pharmacists, including pharmacist-led clinics (4.2%). In 2.8% of surveyed practices, however, 6-monthly follow-up was changed to annual checkup. BP control rates tended to be higher with shared-care teams compared with single-professional-led practices (81.6% vs. 79.5%) and were higher in dispensing versus nondispensing facilities (82.7% vs. 79.7%;  $p < 0.007$ ). In the US, the Veterans Affairs and Kaiser Permanente are two large healthcare systems that have achieved substantial BP control during the last two decades. BP control rates today exceed 80% compared to less than 50% a decade

ago (66,67). This has been achieved through the successful implementation of multicomponent approaches, including physician education, incentives, performance measurements, algorithms, team-based strategies, patient education and patient aids (68–71).

## WHAT SHOULD BE DONE AT FOLLOW-UP VISITS?

Should follow-up visits focus on blood pressure measurement or are other investigations required? Is there guidance on the frequency of such assessments? How is the care of hypertensive patients embedded in management of other cardiovascular risk factors?

The main incentive for achieving long-term optimal BP control lies in the tight relationship between BP and cardiovascular events (72). Hypertension remains a key risk factor for coronary artery disease, cerebrovascular events, left ventricular hypertrophy and congestive heart failure, and contributes to other complications including peripheral artery disease, chronic kidney disease, retinopathy and aortic dissection. Where these conditions are present at first diagnosis of hypertension it may be important to monitor and treat them. In patients without overt target-organ damage, however, one may argue that the risk of developing complications is reasonably low in those with optimally controlled BP.

## INITIAL EVALUATION AND MONITORING AT FOLLOW-UP

Guidelines and healthcare systems differ considerably in their recommendations and resources to support initial evaluation of patients with hypertension. Evidence suggests that ambulatory BP monitoring, serum creatinine, albuminuria and ECG are cornerstones of the workup at first presentation, followed by further tests in cases of abnormal results, in younger patients or where suspicion of secondary hypertension is high. These investigations are in fact the general recommendations in the NICE guidelines (73). Other guidelines, including those by ESH/ESC, also discuss the value of further investigations that look into subclinical organ damage as assessed, for example, by measurement of endothelial function, pulse wave velocity and carotid intima-media thickness (3). Whether an evidence-based minimal workup is employed or if more comprehensive assessments will be performed depends critically on the local setup and the available resources, where the latter are often primarily driven by research interests. In any case, however, the degree of initial workup will often determine the tests and investigations during long-term management, where initial assessments are often more detailed than those at follow-up.

## TREATMENT OF BLOOD PRESSURE AND CARDIOVASCULAR RISK

Hypertension should not be seen in isolation. Management of hypertension should be part of a multifaceted approach

to control cardiovascular risk factors and will therefore extend to management of diabetes, dyslipidaemia, body weight, advice on lifestyle and particularly on smoking cessation. Often these factors will be taken into account in one comprehensive visit in primary care settings, and we have discussed above that such services can benefit from the input of allied healthcare professionals, including pharmacists and nurse specialists, as well as from eHealth and mHealth systems.

In contrast, secondary hypertension services are often specialist clinics that focus on specific areas such as endocrine or renovascular hypertension and are less likely to deliver a holistic approach to the patient but favour specialist diagnosis and treatment of a small range of conditions. It is therefore not possible to provide general recommendations on the extent of risk management in the follow-up of patients with hypertension, but it is important to ensure that at least one member of the wider healthcare team not only addresses BP but also other cardiovascular risk factors; in many cases this will be a primary care physician together with their practice team.

## RECOMMENDED TESTS AND INVESTIGATIONS AT FOLLOW-UP VISITS

The initial phase in the treatment of patients with hypertension will be highly personalised and depends on BP levels, response to treatment and presence of any organ damage. Investigations during this period are often driven by specific therapeutic steps such as assessment of renal function and potassium levels in patients treated with angiotensin-converting enzyme inhibitors or diuretics. Findings beyond high BP such as presence of diabetes or dyslipidaemia will require their own specific follow-up investigations. It is evident that physicians are well aware of such specific investigations that are determined by symptoms and findings from other tests, and seek specialist advice where indicated.

The follow-up of patients after the initial workup and at a time when BP is well controlled, however, remains an area that is less well defined. We have already referred to this in much more detail above when we reviewed the evidence on follow-up intervals, and it is not surprising that clear-cut recommendations on investigations at follow-up are as vague as recommendations on follow-up intervals. It is, however, commonly agreed that the focus of long-term management should lie in cardiovascular risk management and adherence to therapy in addition to assessment of BP and, at intervals, limited investigations into hypertension or treatment-associated complications.

With regard to BP, the majority of patients will not require ambulatory monitoring in the long-term management. Patients with labile hypertension, difficult-to-control hypertension and particularly those with white-coat and masked hypertension will, however, benefit from ambulatory monitoring. Pragmatically, the majority of centres will perform ambulatory BP monitoring on an annual basis. Other important tests at follow-up include assessment of renal function and serum electrolytes (particularly in patients on renin–angiotensin–aldosterone blocking agents), lipids and blood glucose. ECG should be repeated occasionally even if BP control remains optimal, as there may be other features including new-onset atrial fibrillation or prolongation of the QT interval that can be detected.

In our own practice, and this would be in keeping with recommendations of major guidelines (3,4), we assess serum electrolytes, creatinine, glucose or HbA<sub>1c</sub> and albuminuria at least annually, a lipid profile every 2–3 years and ECG every 3–5 years. More important than any rigid investigation schedules, however, is taking the time to update a patient's medical history and to watch out for any symptoms of organ damage, change in BP, and keeping in mind the possibility that patients with essential hypertension are not protected from developing secondary hypertension later in life.

## SUMMARY AND CONCLUSIONS

We are aware that the present chapter provides less detailed information and less specific guidance than other contributions to this book. In summarising the available evidence we have highlighted the lack of robust data and the rather sketchy recommendations in contemporary guidelines, which mainly focus on acute investigations and treatment rather than long-term management.

A few factors should, however, be obvious from the above considerations. First, it generally appears that more frequent follow-up is associated with better adherence, BP control and fewer cardiovascular events. Second, there is no disadvantage to the outcome of patients if follow-up involves or is even led by allied healthcare professionals; in fact, studies have shown that there may be benefits with regard to BP control and risk factor management. The associated cost savings are another factor that should be taken into account. Third, both patients and healthcare professionals realise the potential of eHealth technologies, but their widespread use in routine clinical care is not currently foreseen; weaknesses of available systems include limited user-friendliness, uncertainties about time and cost savings, and the need to fundamentally reorganise clinical services in order to make best and safest use of this potential. Finally, the exact nature of follow-up visits will depend on a number of factors including level of BP control, cardiovascular complications and local and national setup of hypertension services and available resources.

Scientific contributions often end with a statement that further research is needed. Nowhere is this truer in the treatment of patients with hypertension than in follow-up and long-term management. We encourage readers to systematically audit their local practice and develop research proposals into this important area of clinical medicine.

## REFERENCES

1. Chobanian AV, Bakris GL, Black HR et al. The Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC 7 report. *JAMA* 2003; 289: 2560–2572.
2. James PA, Oparil S, Carter BL et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311: 507–520.
3. Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1281–1357.
4. Whelton PK, Carey RM, Aronow WS et al. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for



- the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018; 71(6): e13–e115.
5. Cushman WC, Evans GW et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; 362: 1575–1585.
  6. SPRINT Research Group, Wright JT Jr, Williamson JD et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; 373: 2103–2116.
  7. Fletcher SW, Appel FA, Bourgeois MA. Management of hypertension: Effect of improving patient compliance for follow-up care. *J Am Med Ass* 1975; 233: 242–244.
  8. Roos NR, Carriere KC, Friesen D. Factors influencing the frequency of visits by hypertensive patients to primary care physicians in Winnipeg. *Can Med Ass J* 1998; 159: 777–783.
  9. Guthmann R, Davis N, Brown M, Elizondo J. Visit frequency and hypertension. *J Clin Hypertens* 2005; 7: 327–332.
  10. Turchin A, Goldberg SI, Shubina M et al. Encounter frequency and blood pressure in hypertensive patients with diabetes mellitus. *Hypertension* 2010; 56: 68–74.
  11. Morrison F, Shubina M, Turchin A. Encounter frequency and serum glucose level, blood pressure, and cholesterol level control in patients with diabetes mellitus. *Arch Intern Med* 2011; 171: 1542–1550.
  12. Sherman L, Pelter MA, Deamer RL, Batech M. Association between encounter frequency and time to blood pressure control among newly diagnosed hypertensive patients: A retrospective cohort study. *J Clin Hypertens* 2017, in press.
  13. King CC, Bartels CM, Magnan EM et al. The importance of frequent return visits and hypertension control among US young adults: A multidisciplinary group practice observational study. *J Clin Hypertens (Greenwich)* 2017; 19(12): 1288–1297.
  14. Godwin M, Birtwhistle R, Seguin R et al. Effectiveness of a protocol-based strategy for achieving better blood pressure control in general practice. *Fam Pract* 2010; 27: 55–61.
  15. Birtwhistle RV, Godwin MS, Delva D et al. Randomised equivalence trial comparing three month and six month follow up of patients with hypertension by family practitioners. *BMJ* 2004; 328(7433): 204.
  16. Xu W, Goldberg SI, Shubina M, Turchin A. Optimal systolic blood pressure target, time to intensification, and time to follow-up in treatment of hypertension: Population based retrospective cohort study. *BMJ* 2015; 350: h158, PMID 2565523.
  17. Julius S, Kjeldsen SE, Weber M et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: The VALUE randomised trial. *Lancet* 2004; 363: 2022–2031.
  18. Staessen JA, Thijs L, Fagard R et al. Effects of immediate versus delayed antihypertensive therapy on outcome in the Systolic Hypertension in Europe Trial. *J Hypertens* 2004; 22: 847–857.
  19. Zoungas S, Chalmers J, Neal B et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014; 371: 1392–1406.
  20. Ostbye T, Yarnall KS, Krause KM et al. Is there time for management of patients with chronic diseases in primary care? *Ann Fam Med* 2005; 3: 209–214.
  21. Bodenheimer T. Primary care: Will it survive? *N Engl J Med* 2006; 355: 861–864.
  22. Hauer KE, Durning SJ, Kernan WN. Factors associated with medical students' career choices regarding internal medicine. *J Am Med Ass* 2008; 300: 1154–1164.
  23. Lichtenstein MJ, Sweetnam PM, Elwood PC. Visit frequency for controlled essential hypertension: General practitioners' opinions. *J Fam Pract* 1986; 23: 331–336.
  24. Lichtenstein MJ, Steele MA, Hoehn TP et al. Visit frequency for essential hypertension: Observed associations. *J Fam Pract* 1989; 28: 667–672.
  25. Dunn E, Hilditch J, Chipman M et al. Diagnosis and management of hypertension: The stated practices of family physicians. *Can Med Assoc J* 1984; 130: 985–988.
  26. Fontil V, Bibbins-Domingo K, Kazi D et al. Simulating strategies for improving control of hypertension among patients with usual source of care in the United States: The Blood Pressure Control Model. *J Gen Intern Med* 2015; 30(8): 1147–1155.
  27. Carter BL, Bosworth HB, Green BB. The hypertension team: The role of the pharmacist, nurse, and teamwork in hypertension therapy. *J Clin Hypertens* 2012; 14: 51–65.
  28. Chisholm-Burns MA, Kim Lee J, Spivey CA et al. US pharmacists' effect as team members on patient care: Systematic review and meta-analyses. *Med Care* 2010; 48: 923–933.
  29. Santschi V, Chiolerio A, Burnand B et al. Impact of pharmacist care in the management of cardiovascular disease risk factors: A systematic review and meta-analysis of randomized trials. *Arch Intern Med* 2011; 171: 1441–1453.
  30. Santschi V, Chiolerio A, Paradis G et al. Pharmacist interventions to improve cardiovascular disease risk factors in diabetes: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Care* 2012; 35: 2706–2717.
  31. Blalock SJ, Roberts AW, Lauffenburger JC et al. The effect of community pharmacy-based interventions on patient health outcomes: A systematic review. *Med Care Res Rev* 2013; 70: 235–266.
  32. Santschi V, Chiolerio A, Colosimo AL et al. Improving blood pressure control through pharmacist interventions: A meta-analysis of randomized controlled trials. *J Am Heart Assoc* 2014; 3: e000718.
  33. Greer N, Bolduc J, Geurkink E et al. Pharmacist-led chronic disease management: A systematic review of effectiveness and harms compared with usual care. *Ann Intern Med* 2016; 165: 30–40.
  34. Tsuyuki RT, Houle SKD, Charrois TL et al. Randomized trial of the effect of pharmacist prescribing on improving blood pressure in the community. *Circulation* 2015; 132: 93–100.
  35. Clark CE, Horvath IA, Taylor RS, Campbell JL. Doctors record higher blood pressures than nurses: Systematic review and meta-analysis. *Br J Gen Pract* 2014; 64: e223–e232.
  36. Munding MO. Advanced practice nursing – good medicine for physicians? *N Engl J Med* 1994; 330: 211–214.
  37. Oakeshott P, Kerry S, Austin A, Cappuccio F. Is there a role for nurse-led blood pressure management in primary care? *Fam Pract* 2003; 20: 469–473.
  38. Munding MO, Kane RL, Lemz ER et al. Primary care outcomes in patients treated by nurse practitioners or physicians. *JAMA* 2000; 283: 59–68.
  39. Edelman D, Dolor RJ, Coffman CJ et al. Nurse-led behavioural management of diabetes and hypertension in community practices: A randomized trial. *J Gen Intern Med* 2015; 30(5): 626–633.
  40. Jansink R, Braspenning J, Keizer E et al. No identifiable Hb1Ac or lifestyle change after a comprehensive diabetes programme including motivational interviewing: A cluster randomized trial. *Scand J Prim Health Care* 2013; 31: 119–127.
  41. Blackberry ID, Furler JS, Best JD, Chondros P. Effectiveness of general practice based, practice nurse led telephone coaching on glucemic control of type 2 diabetes. *BMJ* 2013; 347: I5272.
  42. Clark CE, Smith LFP, Taylor RS, Campbell JL. Nurse led interventions to improve control of blood pressure in people with hypertension: Systematic review and meta-analysis. *BMJ* 2010; 341: c3995.
  43. Clark CE, Smith LFP, Taylor RS, Campbell JL. Nurse-led interventions used to improve control of high blood pressure in people with diabetes: A systematic review and meta-analysis. *Diabet Med* 2011; 28: 250–I5261.
  44. Massimi A, De Vito C, Brufola I et al. Are community-based nurse-led self-management support interventions effective in chronic patients? Results of a systematic review and meta-analysis. *PLOS ONE* 2017; 12: e0173617.
  45. McManus RJ, Mant J, Bray EP. Telemonitoring and self-management in the control of hypertension (TASMINH2): A randomised controlled trial. *Lancet* 2010; 376: 163–172.
  46. McLean G, Band R, Saunderson K et al. *J Hypertens* 2016; 34: 600–612.
  47. Widmer RJ, Collins NM, Collins CS et al. Digital health interventions for the prevention of cardiovascular disease: A systematic review and meta-analysis. *Mayo Clin Proc* 2015; 90: 469–480.
  48. de Jongh T, Gurol-Urganci I, Vodopivec-Jamsek V et al. Mobile phone messaging for facilitating self-management of long-term illnesses. *Cochrane Database Syst Rev* 2012; 12: CD007459.
  49. Marquez-Contreras E, de la Figuera M, Gil-Guillen V. Effectiveness of an intervention to provide information to patients with hypertension as short text messages and reminders sent to their mobile phone (HTA alert). *Aten Primaria* 2004; 34: 399–405.
  50. Quinn CC, Clough SS, Minor JM et al. WellDoc mobile diabetes management randomized controlled trial: Change in clinical and behavioral outcomes and patient and physician satisfaction. *Diabetes Technol Ther* 2008; 10: 160–168.
  51. Quinn CC, Shardell MD, Terrin ML et al. Cluster-randomized trial of a mobile phone personalized behavioral intervention for blood glucose control. *Diabetes Care* 2011; 34: 1934–1942.
  52. Liang X, Wang Q, Yang X et al. Effect of mobile phone intervention for diabetes on glycaemic control: A meta-analysis. *Diabet Med* 2011; 28: 455–463.

53. Mobile Medical Applications: Guidance for Food and Drug Administration Staff 2015. <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm263366.pdf> (Accessed 16 November 2017).
54. Kumar N, Khunger M, Gupta A, Garg N. A content analysis of smartphone-based applications for hypertension management. *J Am Soc Hypertens* 2015; 9: 130–136.
55. Plante TB, Urrea B, MacFarlane ZT et al. Validation of the instant blood pressure 54 smartphone app. *JAMA Intern Med* 2016; 176: 700–702.
56. Burke L, Ma J, Azar K et al. Current science on consumer use of mobile health for cardiovascular disease prevention. *Circulation* 2015; 132: 1157–1213.
57. Parati G, Torlasco C, Omboni S, Pellegrini D. Smartphone applications for hypertension management: A potential game-changer that needs more control. *Curr Hypertens Rep* 2017; 19(6): 48.
58. Rossi GP, Bisogni V; European Society of Hypertension Working Group on Endocrine Hypertension. A useful tool to improve the case detection rate of primary aldosteronism: The aldosterone-renin ratio (ARR)-App. *J Hypertens* 2016; 34: 1019–1021.
59. Pawloski PA, Asche SE, Trower NK et al. A substudy evaluating treatment intensification on medication adherence among hypertensive patients receiving home blood pressure telemonitoring and pharmacist management. *J Clin Pharm Ther* 2016; 41: 493–498.
60. Omboni S, Gazzola T, Carabelli G, Parati G. Clinical usefulness and cost effectiveness of home blood pressure telemonitoring: Meta-analysis of randomized controlled studies. *J Hypertens* 2013; 31: 455–467.
61. Duan Y, Xie Z, Dong F et al. Effectiveness of home blood pressure telemonitoring: A systematic review and meta-analysis of randomized controlled studies. *J Hum Hypertens* 2017; 31: 427–437.
62. Asche SE, O'Connor PJ, Dehmer SP et al. Patient characteristics associated with greater blood pressure control in a randomized trial of home blood pressure telemonitoring and pharmacist management. *J Am Soc Hypertens* 2016; 10: 873–880.
63. Wood PW, Boulanger P, Padwal RS. Home blood pressure telemonitoring: Rationale for use, required elements, and barriers to implementation in Canada. *Can J Cardiol* 2017; 33: 619–625.
64. Abdullah A, Liew SM, Hanafi NS et al. What influences patients' acceptance of a blood pressure telemonitoring service in primary care? A Qualitative Study 2016; 10: 99–106.
65. Mejzner N, Clark CE, Smith LF, Campbell JL. Trends in the diagnosis and management of hypertension: Repeated primary care survey in South West England. *Br J Gen Pract* 2017; 67: e306–e313.
66. United States Department of Veteran Affairs 2011. Quality of Care. 2010. <http://www.qualityofcare.va.gov/reports/graph.cfm?CFID=4064909&CFTOKEN=28917425> (Accessed 4 December 2017).
67. Kerr EA, Gerzoff RB, Krein SL et al. Diabetes care quality in the Veterans Affairs Health Care System and commercial managed care: The TRIAD study. *Ann Intern Med* 2004; 141: 272–282.
68. Herck P V, Smedt D D, Annemans L et al. Systematic review: Effects, design choices, and context of pay-for-performance in health care. *BMC Health Serv Res* 2010; 10: 247.
69. Carter BL, Rogers M, Daly J et al. The potency of team-based care interventions for hypertension: A meta-analysis. *Arch Intern Med* 2009; 169: 1748–1755.
70. Glynn LG, Murphy AW, Smith SM et al. Interventions used to improve control of blood pressure in patients with hypertension. *Cochrane Database Syst Rev* 2010; CD005182.
71. Kerr EA, Fleming B. Making performance indicators work: Experiences of US Veterans Health Administration. *BMJ* 2007; 335: 971–973.
72. Lewington S, Clarke R, Qizilbash N et al. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360: 1903–1913.
73. National Institute for Health and Care Excellence. Hypertension in adults: Diagnosis and management. Clinical guideline [CG127] <https://www.nice.org.uk/guidance/cg127> (Accessed 4 December 2017).

# 2018 ESC/ESH GUIDELINES FOR THE MANAGEMENT OF ARTERIAL HYPERTENSION

# 65

THE TASK FORCE FOR THE MANAGEMENT OF ARTERIAL  
HYPERTENSION OF THE EUROPEAN SOCIETY OF CARDIOLOGY  
AND THE EUROPEAN SOCIETY OF HYPERTENSION\*

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## PREAMBLE

Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in selecting the best management strategies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision making of health professionals in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of guidelines have been issued in recent years by the European Society of Cardiology (ESC) and by the European Society of Hypertension (ESH), as well as by other societies and organizations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (<https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines>). ESC and ESH Guidelines represent the official position of the two Societies on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC and ESH to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management of a given condition

according to ESC Committee for Practice Guidelines (CPG) policy and approved by the ESH. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined in [Tables 65.1](#) and [65.2](#).

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (<http://www.escardio.org/guidelines>). Any changes in declarations of interest that arose during the writing period were notified to the ESC and ESH and updated. The Task Force received its entire financial support from the ESC and ESH without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new Guidelines. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts, and in this case by ESH-appointed experts. After appropriate revisions the Guidelines are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG and ESH for publication in the *European Heart Journal* and in the *Journal of Hypertension* as well as in a shortened version in *Blood Pressure*. The Guidelines were developed after careful

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<sup>‡</sup> Professor Zanchetti died toward the end of the development of these Guidelines, in March 2018. He contributed fully to the development of these Guidelines, as a member of the Guidelines' Task Force and as a section co-ordinator. He will be sadly missed by colleagues and friends.

**Table 65.1** ESC classes of recommendations

| Classes of recommendations | Definition                                                                                                                     | Suggested wording to use    |
|----------------------------|--------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Class I                    | Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.                        | Is recommended/is indicated |
| Class II                   | Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.         |                             |
| Class IIa                  | <i>Weight of evidence/opinion is in favour of usefulness/efficacy.</i>                                                         | Should be considered        |
| Class IIb                  | <i>Usefulness/efficacy is less well established by evidence/opinion.</i>                                                       | May be considered           |
| Class III                  | Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful. | Is not recommended          |

**Table 65.2** ESC levels of evidence

|                     |                                                                                              |
|---------------------|----------------------------------------------------------------------------------------------|
| Level of evidence A | Data derived from multiple randomized clinical trials or meta-analyses.                      |
| Level of evidence B | Data derived from a single randomized clinical trial or large non-randomized studies.        |
| Level of evidence C | Consensus of opinion of the experts and/or small studies, retrospective studies, registries. |

consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC and ESH Guidelines also includes the creation of educational tools and implementation programmes for the recommendations including condensed pocket guideline versions, summary slides, booklets with essential messages, summary cards for non-specialists and an electronic version for digital applications (smartphones, APPs, etc.). These versions are abridged and thus, if needed, one should always refer to the full text version, which is freely available via the ESC and ESH websites and hosted on the *European Heart Journal* and *Journal of Hypertension* websites. The National Societies of the ESC are encouraged to endorse, translate and implement all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines, disseminating them, and implementing them into clinical practice.

Health professionals are encouraged to take the ESC and ESH Guidelines fully into account when exercising their clinical judgement, as well as in the determination and the implementation of preventive, diagnostic, or therapeutic medical strategies. However, the ESC and ESH Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

## INTRODUCTION

Substantial progress has been made in understanding the epidemiology, pathophysiology and risk associated with hypertension, and a wealth of evidence exists to demonstrate that lowering blood pressure (BP) can substantially reduce premature morbidity and mortality [1–10]. A number of proven, highly effective, and well tolerated lifestyle and drug treatment strategies can achieve this reduction in BP. Despite this, BP control rates remain poor worldwide and are far from satisfactory across Europe. Consequently, hypertension remains the major preventable cause of cardiovascular disease (CVD) and all-cause death globally and in our continent [11–14].

These 2018 ESC/ESH Guidelines for the management of arterial hypertension are designed for adults with hypertension, that is, aged at least 18 years. The purpose of the review and update of these Guidelines was to evaluate and incorporate new evidence into the Guideline recommendations. The specific aims of these Guidelines were to produce pragmatic recommendations to improve the detection and treatment of hypertension and to improve the poor rates of BP control by promoting simple and effective treatment strategies.

These joint 2018 Guidelines follow the same principles upon which a series of hypertension Guidelines were jointly issued by the two societies in 2003, 2007 and 2013. These fundamental principles are to base recommendations on properly conducted studies, identified from an extensive review of the literature; to give the highest priority to data from randomized controlled trials (RCTs); to also consider well conducted meta-analyses of RCTs as strong evidence (this contrasts with network meta-analyses, which we do not consider to have the same level of evidence because many of the comparisons are nonrandomized); to recognize that RCTs cannot address many important questions related to the diagnosis, risk stratification and treatment of hypertension, which can be addressed by observational or registry-based studies of appropriate scientific calibre; to grade the level of scientific evidence and the strength of recommendations according to ESC recommendations (see section 'Preamble'); to recognize that opinions may differ on key recommendations, which are resolved by voting; and to recognize that there are circumstances in which there is inadequate or no evidence, but that the question is important for clinical practice and cannot be ignored. In these circumstances, we resort to pragmatic expert opinion and endeavour to explain its rationale.

Each member of the Task Force was assigned specific writing tasks, which were reviewed by section co-ordinators and then by the two chairs, one appointed by the ESC and the other by the ESH. The text was developed over approximately 24 months, during which the Task Force members

met collectively and corresponded intensively with one another between meetings. Before publication, the document was reviewed by European reviewers selected by the ESC and ESH, and by representatives of ESC National Cardiac Societies and ESH National Hypertension Societies.

## WHAT IS NEW AND WHAT HAS CHANGED IN THE 2018 ESC/ESH ARTERIAL HYPERTENSION GUIDELINES?

| Changes in recommendations                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2013                                                                                                                                                                                                                                                                                                                                                                        | 2018                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Diagnosis                                                                                                                                                                                                                                                                                                                                                                   | Diagnosis                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Office BP is recommended for screening and diagnosis of hypertension.                                                                                                                                                                                                                                                                                                       | It is recommended to base the diagnosis of hypertension on: <ul style="list-style-type: none"> <li>■ Repeated office BP measurements; or</li> <li>■ Out-of-office BP measurement with ABPM and/or HBPM if logistically and economically feasible.</li> </ul>                                                                                                                                                                             |
| Treatment thresholds                                                                                                                                                                                                                                                                                                                                                        | Treatment thresholds                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>High-normal BP (130–139/85–89 mmHg):</b> Unless the necessary evidence is obtained, it is not recommended to initiate antihypertensive drug therapy at high-normal BP.                                                                                                                                                                                                   | <b>High-normal BP (130–139/85–89 mmHg):</b> Drug treatment may be considered when cardiovascular risk is very high due to established CVD, especially CAD.                                                                                                                                                                                                                                                                               |
| Treatment thresholds                                                                                                                                                                                                                                                                                                                                                        | Treatment thresholds                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Treatment of low-risk grade 1 hypertension:</b> Initiation of antihypertensive drug treatment should also be considered in grade 1 hypertensive patients at low-moderate risk, when BP is within this range at several repeated visits or elevated by ambulatory BP criteria, and remains within this range despite a reasonable period of time with lifestyle measures. | <b>Treatment of low-risk grade 1 hypertension:</b> In patients with grade 1 hypertension at low-moderate-risk and without evidence of HMOD, BP-lowering drug treatment is recommended if the patient remains hypertensive after a period of lifestyle intervention.                                                                                                                                                                      |
| Treatment thresholds                                                                                                                                                                                                                                                                                                                                                        | Treatment thresholds                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Older patients</b><br>Antihypertensive drug treatment may be considered in the elderly (at least when younger than 80 years) when SBP is in the 140–159 mmHg range, provided that antihypertensive treatment is well tolerated.                                                                                                                                          | <b>Older patients</b><br>BP-lowering drug treatment and lifestyle intervention is recommended in fit older patients (>65 years but not >80 years) when SBP is in the grade 1 range (140–159 mmHg), provided that treatment is well tolerated.                                                                                                                                                                                            |
| BP treatment targets                                                                                                                                                                                                                                                                                                                                                        | BP treatment targets                                                                                                                                                                                                                                                                                                                                                                                                                     |
| An SBP goal of <140 mmHg is recommended.                                                                                                                                                                                                                                                                                                                                    | <ul style="list-style-type: none"> <li>■ It is recommended that the first objective of treatment should be to lower BP to &lt;140/90 mmHg in all patients and, provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients.</li> <li>■ In patients &lt;65 years it is recommended that SBP should be lowered to a BP range of 120–129 mmHg in most patients.</li> </ul> |
| BP treatment targets in older patients (65–80 years)                                                                                                                                                                                                                                                                                                                        | BP treatment targets in older patients (65–80 years)                                                                                                                                                                                                                                                                                                                                                                                     |
| An SBP target of between 140–150 mmHg is recommended for older patients (65–80 years).                                                                                                                                                                                                                                                                                      | In older patients (≥65 years), it is recommended that SBP should be targeted to a BP range of 130–139 mmHg.                                                                                                                                                                                                                                                                                                                              |
| BP treatment targets in patients aged over 80 years                                                                                                                                                                                                                                                                                                                         | BP treatment targets in patients aged over 80 years                                                                                                                                                                                                                                                                                                                                                                                      |
| An SBP target between 140–150 mmHg should be considered in people older than 80 years, with an initial SBP ≥160 mmHg, provided that they are in good physical and mental condition.                                                                                                                                                                                         | An SBP target range of 130–139 mmHg is recommended for people older than 80 years, if tolerated.                                                                                                                                                                                                                                                                                                                                         |
| DBP targets                                                                                                                                                                                                                                                                                                                                                                 | DBP targets                                                                                                                                                                                                                                                                                                                                                                                                                              |
| A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended.                                                                                                                                                                                                                                                  | A DBP target of <80 mmHg should be considered for all hypertensive patients, independent of the level of risk and comorbidities.                                                                                                                                                                                                                                                                                                         |

*Continued*



|                                                                                                                                                                 |                |                                                                                                                                                                                                                                                                                                                                               |                  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| <b>Initiation of drug treatment</b>                                                                                                                             |                | <b>Initiation of drug treatment</b>                                                                                                                                                                                                                                                                                                           |                  |
| Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline BP or at high cardiovascular risk. |                | It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in a SPC. The exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is <150 mmHg).                                                                                                 |                  |
| <b>Resistant hypertension</b>                                                                                                                                   |                | <b>Resistant hypertension</b>                                                                                                                                                                                                                                                                                                                 |                  |
| Mineralocorticoid receptor antagonists, amiloride, and the alpha-1 blocker doxazosin should be considered if no contraindication exists.                        |                | Recommended treatment of resistant hypertension is the addition of low-dose spironolactone to existing treatment, or the addition of further diuretic therapy if intolerant to spironolactone, with either eplerenone, amiloride, higher-dose thiazide/thiazide-like diuretic or a loop diuretic, or the addition of bisoprolol or doxazosin. |                  |
| <b>Device-based therapy for hypertension</b>                                                                                                                    |                | <b>Device-based therapy for hypertension</b>                                                                                                                                                                                                                                                                                                  |                  |
| In case of ineffectiveness of drug treatment, invasive procedures such as renal denervation and baroreceptor stimulation may be considered.                     |                | Use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available.                                                                                                                 |                  |
| <b>Recommendation Grading</b>                                                                                                                                   |                |                                                                                                                                                                                                                                                                                                                                               |                  |
|                                                                                                                                                                 | <b>Grade I</b> | <b>Grade IIa</b>                                                                                                                                                                                                                                                                                                                              | <b>Grade IIb</b> |
|                                                                                                                                                                 |                |                                                                                                                                                                                                                                                                                                                                               | <b>Grade III</b> |

*Abbreviations:* ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CAD, coronary artery disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; HBPM, home blood pressure monitoring; HMOD, hypertension-mediated organ damage; RCT, randomized controlled trial; SBP, systolic blood pressure; SPC, single-pill combination.

|                                                                                                                                                                                                                                                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>New sections/recommendations</b>                                                                                                                                                                                                                             |
| When to suspect and how to screen for the causes of secondary hypertension                                                                                                                                                                                      |
| Management of hypertension emergencies                                                                                                                                                                                                                          |
| Updated recommendations on the management of BP in acute stroke                                                                                                                                                                                                 |
| Updated recommendations on the management of hypertension in women and pregnancy                                                                                                                                                                                |
| Hypertension in different ethnic groups                                                                                                                                                                                                                         |
| The effects of altitude on BP                                                                                                                                                                                                                                   |
| Hypertension and chronic obstructive pulmonary disease                                                                                                                                                                                                          |
| Hypertension and AF and other arrhythmias                                                                                                                                                                                                                       |
| Oral anticoagulant use in hypertension                                                                                                                                                                                                                          |
| Hypertension and sexual dysfunction                                                                                                                                                                                                                             |
| Hypertension and cancer therapies                                                                                                                                                                                                                               |
| Perioperative management of hypertension                                                                                                                                                                                                                        |
| Glucose-lowering drugs and BP                                                                                                                                                                                                                                   |
| Updated recommendations on cardiovascular risk assessment and management: using the SCORE system to assess risk in patients without CVD; the importance of HMOD in modifying cardiovascular risk; and the use of statins and aspirin for CVD prevention         |
| <b>New concepts</b>                                                                                                                                                                                                                                             |
| <b>BP measurement</b>                                                                                                                                                                                                                                           |
| <b>Wider use of out-of-office BP measurement with ABPM and/or HBPM</b> , especially HBPM, as an option to confirm the diagnosis of hypertension, detect white-coat and masked hypertension and monitor BP control                                               |
| <b>Less conservative treatment of BP in older and very old patients</b>                                                                                                                                                                                         |
| <b>Lower BP thresholds and treatment targets for older patients</b> , with emphasis on considerations of biological rather than chronological age (i.e. the importance of frailty, independence, and the tolerability of treatment)                             |
| Recommendation that treatment should never be denied or withdrawn on the basis of age, provided that treatment is tolerated                                                                                                                                     |
| <b>A SPC treatment strategy to improve BP control</b>                                                                                                                                                                                                           |
| <b>Preferred use of two-drug combination</b> therapy for the initial treatment of most people with hypertension                                                                                                                                                 |
| <b>A single-pill treatment strategy for hypertension</b> with the preferred use of SPC therapy for most patients                                                                                                                                                |
| <b>Simplified drug treatment algorithms</b> with the preferred use of an ACE inhibitor or ARB, combined with a CCB and/or a thiazide/thiazide-like diuretic, as the core treatment strategy for most patients, with beta-blockers used for specific indications |

Continued

**New target ranges for BP in treated patients**

**Target BP ranges for treated patients** to better identify the recommended BP target and **lower safety boundaries for treated BP**, according to a patient's age and specific comorbidities

**Detecting poor adherence to drug therapy**

A strong emphasis on the **importance of evaluating treatment adherence** as a major cause of poor BP control

**A key role for nurses and pharmacists in the longer-term management of hypertension**

**The important role of nurses and pharmacists** in the education, support, and follow-up of treated hypertensive patients is emphasized as part of the overall strategy to improve BP control

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; HBPM, home blood pressure monitoring; HMOD, hypertension-mediated organ damage; SCORE, Systematic COronary Risk Evaluation; SPC, single-pill combination.

## DEFINITION, CLASSIFICATION, AND EPIDEMIOLOGICAL ASPECTS OF HYPERTENSION

### DEFINITION OF HYPERTENSION

The relationship between BP and cardiovascular and renal events is continuous, making the distinction between normotension and hypertension, based on cut-off BP values, somewhat arbitrary [2,4,8]. However, in practice, cut-off BP values are used for pragmatic reasons to simplify the diagnosis and decisions about treatment. Epidemiological associations between BP and cardiovascular risk extend from very low levels of BP (i.e. SBP >115 mmHg). However, 'hypertension' is defined as the level of BP at which the benefits of treatment (either with lifestyle interventions or drugs) unequivocally outweigh the risks of treatment, as documented by clinical trials. This evidence has been reviewed (see section 'When to initiate antihypertensive treatment' for detailed discussion of hypertension diagnostic thresholds) and provides the basis for the recommendation that the classification of BP and definition of hypertension remain unchanged from previous ESH/ESC Guidelines (Table 65.3) [15–17].

Hypertension is defined as office SBP values at least 140 mmHg and/or diastolic BP (DBP) values at least 90 mmHg. This is based on evidence from multiple RCTs that treatment of patients with these BP values is beneficial (see section 'Treatment of hypertension'). The same classification is used in younger, middle-aged, and older people, whereas BP centiles are used in children and teenagers, in whom data from interventional trials are not available. Details on BP classification in boys and girls 16 years or less of age can be found in the 2016 ESH Guidelines for children and adolescents [18].

### CLASSIFICATION OF BLOOD PRESSURE

| Classification of BP                                                                                                         |                    |                    |
|------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Recommendation                                                                                                               | Class <sup>a</sup> | Level <sup>b</sup> |
| It is recommended that BP be classified as optimal, normal, high-normal, or grades 1–3 hypertension, according to office BP. | <b>I</b>           | <b>C</b>           |

Abbreviation: BP, blood pressure.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

**Table 65.3** Classification of office blood pressure<sup>a</sup> and definitions of hypertension grade<sup>b</sup>

| Category                                    | Systolic (mmHg) |        | Diastolic (mmHg) |
|---------------------------------------------|-----------------|--------|------------------|
| Optimal                                     | <120            | and    | <80              |
| Normal                                      | 120–129         | and/or | 80–84            |
| High normal                                 | 130–139         | and/or | 85–89            |
| Grade 1 hypertension                        | 140–159         | and/or | 90–99            |
| Grade 2 hypertension                        | 160–179         | and/or | 100–109          |
| Grade 3 hypertension                        | ≥180            | and/or | ≥110             |
| Isolated systolic hypertension <sup>b</sup> | ≥140            | and    | <90              |

Abbreviation: BP, blood pressure.

<sup>a</sup> BP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic.

<sup>b</sup> Isolated systolic hypertension is graded 1, 2, or 3 according to systolic BP values in the ranges indicated. The same classification is used for all ages from 16 years.

### PREVALENCE OF HYPERTENSION

Based on office BP, the global prevalence of hypertension was estimated to be 1.13 billion in 2015 [5], with a prevalence of over 150 million in central and Eastern Europe. The overall prevalence of hypertension in adults is around 30–45% [12], with a global age-standardized prevalence of 24 and 20% in men and women, respectively, in 2015 [5]. This high prevalence of hypertension is consistent across the world, irrespective of income status, that is in lower, middle and higher income countries [12]. Hypertension becomes progressively more common with advancing age, with a prevalence of more than 60% in people aged more than 60 years [12]. As populations age, adopt more sedentary lifestyles, and increase their body weight, the prevalence of hypertension worldwide will continue to rise. It is estimated that the number of people with hypertension will increase by 15–20% by 2025, reaching close to 1.5 billion [19].

## BLOOD PRESSURE RELATIONSHIP WITH RISK OF CARDIOVASCULAR AND RENAL EVENTS

Elevated BP was the leading global contributor to premature death in 2015, accounting for almost 10 million deaths and over 200 million disability-adjusted life years [3]. Importantly, despite advances in diagnosis and treatment over the past 30 years, the disability-adjusted life years attributable to hypertension have increased by 40% since 1990 [3]. SBP at least 140 mmHg accounts for most of the mortality and disability burden (70%), and the largest number of SBP-related deaths per year are due to ischaemic heart disease (4.9 million), haemorrhagic stroke (2.0 million), and ischaemic stroke (1.5 million) [3].

Both office BP and out-of-office BP have an independent and continuous relationship with the incidence of several cardiovascular events [haemorrhagic stroke, ischaemic stroke, myocardial infarction, sudden death, heart failure, and peripheral artery disease (PAD)], as well as end-stage renal disease [4]. Accumulating evidence is closely linking hypertension with an increased risk of developing atrial fibrillation (AF) [20], and evidence is emerging that links early elevations of BP to increased risk of cognitive decline and dementia [21,22].

The continuous relationship between BP and risk of events has been shown at all ages [23] and in all ethnic groups [24,25], and extends from high BP levels to relatively low values. SBP appears to be a better predictor of events than DBP after the age of 50 years [23,26,27]. High DBP is associated with increased cardiovascular risk and is more commonly elevated in younger (<50 years) vs. older patients. DBP tends to decline from midlife as a consequence of arterial stiffening; consequently, SBP assumes even greater importance as a risk factor from midlife [26]. In middle-aged and older people, increased pulse pressure (the difference between SBP and DBP values) has additional adverse prognostic significance [28,29].

## HYPERTENSION AND TOTAL CARDIOVASCULAR RISK ASSESSMENT

Hypertension rarely occurs in isolation, and often clusters with other cardiovascular risk factors such as dyslipidaemia and glucose intolerance [30,31]. This metabolic risk factor clustering has a multiplicative effect on cardiovascular risk [32]. Consequently, quantification of total cardiovascular risk (i.e. the likelihood of a person developing a cardiovascular event over a defined period) is an important part of the risk stratification process for patients with hypertension. Many cardiovascular risk assessment systems are available and most project 10-year risk. Since 2003, the European Guidelines on CVD prevention have recommended use of the Systematic COronary Risk Evaluation (SCORE) system because it is based on large, representative European cohort data sets (available at: <http://www.escardio.org/Guidelines-&-Education/Practice-tools/CVD-prevention-toolbox/SCORE-Risk-Charts>). The SCORE system estimates the 10-year risk of a first fatal atherosclerotic event, in relation to age, sex, smoking habits, total cholesterol level, and SBP. The SCORE system also allows calibration for different cardiovascular risk levels across numerous European countries and has been externally validated [33]. A previous limitation of the SCORE system was

that it applied only to patients aged 40–65 years; however, the SCORE system has recently been adapted for patients over the age of 65 years [34]. Detailed information on cardiovascular risk assessment is available [35].

Factors influencing cardiovascular risk factors in patients with hypertension are shown in Table 65.4. Hypertensive patients with documented CVD, including asymptomatic atheromatous disease on imaging, type 1 or type 2 diabetes, very high levels of individual risk factors (including grade 3 hypertension), or chronic kidney disease (CKD; stages 3–5), are automatically considered to be at very high (i.e. 10% CVD mortality) or high (i.e. 5–10% CVD mortality) 10 year cardiovascular risk (Table 65.5). Such patients do not need formal cardiovascular risk estimation to determine their need for treatment of their hypertension and other cardiovascular risk factors. For all other hypertensive patients, estimation of 10-year cardiovascular risk using the SCORE system is recommended. Estimation should be complemented by assessment of hypertension-mediated organ damage (HMOD), which can also increase cardiovascular risk to a higher level, even when asymptomatic (see Table 65.4 and sections ‘Importance of hypertension-mediated organ damage in refining cardiovascular risk assessment in hypertensive patients’ and ‘Blood pressure measurement’).

There is also emerging evidence that an increase in serum uric acid to levels lower than those typically associated with gout is independently associated with increased cardiovascular risk in both the general population and in hypertensive patients. Measurement of serum uric acid is recommended as part of the screening of hypertensive patients [36].

The SCORE system only estimates the risk of fatal cardiovascular events. The risk of total cardiovascular events (fatal and nonfatal) is approximately three times higher than the rate of fatal cardiovascular events in men and four times higher in women. This multiplier is attenuated to less than three times in older people in whom a first event is more likely to be fatal [37].

There are important general modifiers of cardiovascular risk (Table 65.6) as well as specific cardiovascular risk modifiers for patients with hypertension. Cardiovascular risk modifiers are particularly important at the cardiovascular risk boundaries, and especially for patients at moderate-risk in whom a risk modifier might convert moderate-risk to high risk and influence treatment decisions with regard to cardiovascular risk factor management. Furthermore, cardiovascular risk estimates by the SCORE system may be modified in first-generation immigrants to Europe and cardiovascular risk scores in such patients may be adjusted by correction factors (Table 65.7). Further details of the impact of cardiovascular risk modifiers are available from the ESC 2016 CVD prevention Guidelines [35].

## IMPORTANCE OF HYPERTENSION-MEDIATED ORGAN DAMAGE IN REFINING CARDIOVASCULAR RISK ASSESSMENT IN HYPERTENSIVE PATIENTS

A unique and important aspect of cardiovascular risk estimation in hypertensive patients is the need to consider the impact of HMOD. This was previously termed ‘target-organ damage’, but HMOD more accurately describes hypertension-induced structural and/or functional changes in major organs (i.e. the heart, brain, retina, kidney, and vasculature) (Table 65.4). There are three important

**Table 65.4** Factors influencing cardiovascular risk in patients with hypertension

| Demographic characteristics and laboratory parameters                                                                                                                                                                                                                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sex <sup>a</sup> (men >women)                                                                                                                                                                                                                                                 |
| Age <sup>a</sup>                                                                                                                                                                                                                                                              |
| Smoking (current or past history) <sup>a</sup>                                                                                                                                                                                                                                |
| Total cholesterol <sup>a</sup> and HDL-C                                                                                                                                                                                                                                      |
| Uric acid                                                                                                                                                                                                                                                                     |
| Diabetes <sup>a</sup>                                                                                                                                                                                                                                                         |
| Overweight or obesity                                                                                                                                                                                                                                                         |
| Family history of premature CVD (men aged <55 years and women aged <65 years)                                                                                                                                                                                                 |
| Family or parental history of early-onset hypertension                                                                                                                                                                                                                        |
| Early-onset menopause                                                                                                                                                                                                                                                         |
| Sedentary lifestyle                                                                                                                                                                                                                                                           |
| Psychosocial and socioeconomic factors                                                                                                                                                                                                                                        |
| Heart rate (resting values >80 beats/min)                                                                                                                                                                                                                                     |
| Asymptomatic HMOD                                                                                                                                                                                                                                                             |
| Arterial stiffening:<br>Pulse pressure (in older people) 60 mmHg<br>Carotid–femoral PWV >10 m/s                                                                                                                                                                               |
| ECG LVH (Sokolow–Lyon index >35 mm, or R in aVL ≥11 mm; Cornell voltage duration product >2440 mm*ms, or Cornell voltage >28 mm in men or >20 mm in women)                                                                                                                    |
| Echocardiographic LVH [left ventricular mass index: men >50 g/m <sup>2.7</sup> ; women >47 g/m <sup>2.7</sup> (height in m <sup>2.7</sup> ); indexation for BSA may be used in normal-weight patients; left ventricular mass/BSA g/m <sup>2</sup> >115 (men) and >95 (women)] |
| Microalbuminuria (30–300 mg/24 h), or elevated albumin–creatinine ratio (30–300 mg/g; 3.4–34 mg/mmol) (preferentially on morning spot urine) <sup>b</sup>                                                                                                                     |
| Moderate CKD with eGFR 30–59 mL/min/1.73 m <sup>2</sup> (BSA) <sup>b</sup>                                                                                                                                                                                                    |
| Ankle-brachial index <0.9                                                                                                                                                                                                                                                     |
| Advanced retinopathy: haemorrhages or exudates, papilloedema                                                                                                                                                                                                                  |
| Established cardiovascular or renal disease                                                                                                                                                                                                                                   |
| Cerebrovascular disease: ischaemic stroke, cerebral haemorrhage, TIA                                                                                                                                                                                                          |
| CAD: myocardial infarction, angina, myocardial revascularization                                                                                                                                                                                                              |
| Presence of atheromatous plaque on imaging                                                                                                                                                                                                                                    |
| Heart failure, including HFpEF                                                                                                                                                                                                                                                |
| Peripheral artery disease                                                                                                                                                                                                                                                     |
| Atrial fibrillation                                                                                                                                                                                                                                                           |
| Severe CKD with eGFR <30 mL/min/1.73 m <sup>2</sup>                                                                                                                                                                                                                           |

Abbreviations: BSA, body surface area; CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, HDL cholesterol; HFpEF, heart failure with preserved ejection fraction; HMOD, hypertension-mediated organ damage; LVH, left ventricular hypertrophy; PWV, pulse wave velocity; SCORE, Systematic COronary Risk Evaluation; TIA, transient ischaemic attack.

<sup>a</sup> CV risk factors included in the SCORE system.

<sup>b</sup> Proteinuria and reduced eGFR are independent risk factors. See Table 65.6 for cardiovascular risk modifiers.

considerations: not all features of HMOD are included in the SCORE system (CKD and established vascular disease are included) and several hypertensive HMODs (e.g. cardiac, vascular, and retinal) have well established adverse prognostic significance (see section ‘Clinical evaluation and assessment of hypertension-mediated organ damage in patients with hypertension’) and may, especially if HMOD is pronounced, lead to a high cardiovascular risk even in the absence of classical cardiovascular risk factors; the presence of HMOD is common and often goes undetected [38]; and the presence of multiple HMODs in the same patient is also common, and further increases cardiovascular risk [39–41]. Consequently, the inclusion of HMOD assessment is important in patients with

hypertension and helps identify high-risk or very high-risk hypertensive patients who may otherwise be misclassified as having a lower level of risk by the SCORE system [42]. This is especially true for the presence of left ventricular hypertrophy (LVH), CKD with albuminuria or proteinuria, or arterial stiffening [43] (see section ‘Clinical evaluation and assessment of hypertension-mediated organ damage in patients with hypertension’). The impact of progression of the stages of hypertension-associated disease (from uncomplicated through to asymptomatic or established disease), according to different grades of hypertension and the presence of cardiovascular risk factors, HMOD, or comorbidities, is illustrated in Figure 65.1 for middle-aged individuals.

**Table 65.5** Ten-year cardiovascular risk categories (Systematic COronary Risk Evaluation system)

|                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Very high risk</b> | <b>People with any of the following:</b><br><b>Documented CVD, either clinical or unequivocal on imaging.</b> <ul style="list-style-type: none"> <li>■ <b>Clinical CVD</b> includes acute myocardial infarction, acute coronary syndrome, coronary or other arterial revascularization, stroke, TIA, aortic aneurysm, and PAD</li> <li>■ <b>Unequivocal documented CVD on imaging</b> includes significant plaque (i.e. <math>\geq 50\%</math> stenosis) on angiography or ultrasound; it does not include increase in carotid intima-media thickness</li> <li>■ <b>Diabetes mellitus with target-organ damage</b>, e.g. proteinuria or a with a major risk factor such as grade 3 hypertension or hypercholesterolaemia</li> <li>■ <b>Severe CKD</b> (eGFR <math>&lt; 30</math> mL/min/1.73 m<sup>2</sup>)</li> <li>■ <b>A calculated 10-year SCORE of <math>\geq 10\%</math></b></li> </ul> |
| <b>High risk</b>      | <b>People with any of the following:</b> <ul style="list-style-type: none"> <li>■ <b>Marked elevation of a single risk factor</b>, particularly cholesterol <math>&gt; 8</math> mmol/L (<math>&gt; 310</math> mg/dL), e.g. familial hypercholesterolaemia or grade 3 hypertension (BP <math>\geq 180/110</math> mmHg)</li> <li>■ <b>Most other people with diabetes mellitus</b> (except some young people with type 1 diabetes mellitus and without major risk factors, who may be at moderate risk)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                              |
|                       | <b>Hypertensive LVH</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                       | <b>Moderate CKD (eGFR 30–59 mL/min/1.73 m<sup>2</sup>)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                       | <b>A calculated 10-year SCORE of 5–10%</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Moderate risk</b>  | <b>People with:</b> <ul style="list-style-type: none"> <li>■ <b>A calculated 10-year SCORE of <math>\geq 1</math> to <math>&lt; 5\%</math></b></li> <li>■ <b>Grade 2 hypertension</b></li> <li>■ <b>Many middle-aged people belong to this category</b></li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Low risk</b>       | <b>People with:</b> <ul style="list-style-type: none"> <li>■ <b>A calculated 10-year SCORE of <math>&lt; 1\%</math></b></li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LVH, left ventricular hypertrophy; TIA, transient ischaemic attack; PAD, peripheral artery disease; SCORE, Systematic COronary Risk Evaluation.

**Table 65.6** Risk modifiers increasing cardiovascular risk estimated by the Systemic COronary Risk Evaluation (SCORE) system

|                                                                                                  |
|--------------------------------------------------------------------------------------------------|
| Social deprivation, the origin of many causes of CVD                                             |
| Obesity (measured by BMI) and central obesity (measured by waist circumference)                  |
| Physical inactivity                                                                              |
| Psychosocial stress, including vital exhaustion                                                  |
| Family history of premature CVD (occurring at age $< 55$ years in men and $< 60$ years in women) |
| Autoimmune and other inflammatory disorders                                                      |
| Major psychiatric disorders                                                                      |
| Treatment for infection with human immunodeficiency virus                                        |
| Atrial fibrillation                                                                              |
| Left ventricular hypertrophy                                                                     |
| CKD                                                                                              |
| Obstructive sleep apnoea syndrome                                                                |

Source: Piepoli MF et al. Eur Heart J 2016;37:2315–2381.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease.

**Table 65.7** Correction factors for the Systemic COronary Risk Evaluation (SCORE) cardiovascular risk estimates in first-generation immigrants to Europe

| Region of origin   | Multiplication factor |
|--------------------|-----------------------|
| Southern Asia      | 1.4                   |
| Sub-Saharan Africa | 1.3                   |
| Caribbean          | 1.3                   |
| Western Asia       | 1.2                   |
| Northern Africa    | 0.9                   |
| Eastern Asia       | 0.7                   |
| Southern America   | 0.7                   |

Source: Piepoli MF et al. Eur Heart J 2016;37:2315–2381.

## CHALLENGES IN CARDIOVASCULAR RISK ASSESSMENT

Cardiovascular risk is strongly influenced by age (i.e. older people are invariably at high absolute cardiovascular risk). In contrast, the absolute risk of younger people, particularly younger women, is invariably low, even in those with a markedly abnormal risk factor profile. In the latter,



| Hypertension disease staging      | Other risk factors, HMOD, or disease                                   | BP (mmHg) grading                       |                                     |                                       |                                    |
|-----------------------------------|------------------------------------------------------------------------|-----------------------------------------|-------------------------------------|---------------------------------------|------------------------------------|
|                                   |                                                                        | High normal<br>SBP 130–139<br>DBP 85–89 | Grade 1<br>SBP 140–159<br>DBP 90–99 | Grade 2<br>SBP 160–179<br>DBP 100–109 | Grade 3<br>SBP ≥180<br>or DBP ≥110 |
| Stage 1<br>(uncomplicated)        | No other risk factors                                                  | Low risk                                | Low risk                            | Moderate risk                         | High risk                          |
|                                   | 1 or 2 risk factors                                                    | Low risk                                | Moderate risk                       | Moderate to high risk                 | High risk                          |
|                                   | ≥ 3 risk factors                                                       | Low to Moderate risk                    | Moderate to high risk               | High Risk                             | High risk                          |
| Stage 2<br>(asymptomatic disease) | HMOD, CKD grade 3, or diabetes mellitus without organ damage           | Moderate to high risk                   | High risk                           | High risk                             | High to very high risk             |
| Stage 3<br>(established disease)  | Established CVD, CKD grade ≥ 4, or diabetes mellitus with organ damage | Very high risk                          | Very high risk                      | Very high risk                        | Very high risk                     |

**Figure 65.1** Classification of hypertension stages according to blood pressure levels, presence of cardiovascular risk factors, hypertension-mediated organ damage, or comorbidities. Cardiovascular risk is illustrated for a middle-aged male. The cardiovascular risk does not necessarily correspond to the actual risk at different ages. The use of the SCORE system is recommended for formal estimation of cardiovascular risk for treatment decisions. *Abbreviations:* BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; HMOD, hypertension-mediated organ damage; SBP, systolic blood pressure; SCORE, Systematic COronary Risk Evaluation.

relative risk is elevated even if absolute risk is low. The use of ‘cardiovascular risk age’ has been proposed as a useful way of communicating risk and making treatment decisions, especially for younger people at low absolute risk but with high relative risk [35]. This works by illustrating how a younger patient (e.g. a 40-year-old) with risk factors but low absolute risk has a cardiovascular risk equivalent to a much older person (60 years) with optimal risk factors; thus, the cardiovascular risk age of the younger patient is 60 years. The cardiovascular risk age can be automatically calculated using HeartScore ([www.heartscore.org](http://www.heartscore.org)).

A second consideration is that the presence of concomitant disease is often recorded in a binary way in cardiovascular risk assessment systems (e.g. diabetes, yes/no). This does not reflect the impact of the severity or duration of concomitant diseases on total cardiovascular risk. For example, long-standing diabetes is clearly associated with high risk, whereas the risk is less certain for recent-onset diabetes [34].

A third conundrum specific to hypertension is what BP value to use in cardiovascular risk assessment in a patient who is receiving treatment for hypertension. If treatment was commenced recently, it seems appropriate to use the pretreatment BP value. If treatment has been long-standing, using the current treated BP value will invariably underestimate risk because it does not reflect prior longer-term exposure to higher BP levels, and antihypertensive treatment does not completely reverse the risk even when BP is well controlled. If treatment has been long-standing, then the ‘treated BP value’ should be used, with the caveat that the calculated cardiovascular risk will be lower than the patient’s actual risk. A fourth conundrum is how to

impute out-of-office BP values into risk calculators that have been calibrated according to office BP readings. These various limitations should be kept in mind when estimating cardiovascular risk in clinical practice.

#### Hypertension and cardiovascular risk assessment

| Recommendation                                                                                                                                                                                                                                                              | Class <sup>a</sup> | Level <sup>b</sup> |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| CV risk assessment with the SCORE system is recommended for hypertensive patients who are not already at high or very high risk due to established CVD, renal disease, or diabetes, a markedly elevated single risk factor (e.g. cholesterol), or hypertensive LVH [33,35]. | I                  | B                  |

*Abbreviations:* CVD, cardiovascular disease; LVH, left ventricular hypertrophy; SCORE, Systematic COronary Risk Evaluation.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

## BLOOD PRESSURE MEASUREMENT

### CONVENTIONAL OFFICE BLOOD PRESSURE MEASUREMENT

Auscultatory or oscillometric semiautomatic or automatic sphygmomanometers are the preferred method for measuring BP in the doctor’s office. These devices should be

validated according to standardized conditions and protocols [44]. BP should initially be measured in both upper arms, using an appropriate cuff size for the arm circumference. A consistent and significant SBP difference between arms (i.e.  $>15$  mmHg) is associated with an increased cardiovascular risk [45], most likely due to atheromatous vascular disease. Where there is a difference in BP between arms, ideally established by simultaneous measurement, the arm with the higher BP values should be used for all subsequent measurements.

In older people, people with diabetes, or people with other causes of orthostatic hypotension, BP should also be measured 1 and 3 min after standing. Orthostatic hypotension is defined as a reduction in SBP of at least 20 mmHg or in DBP of at least 10 mmHg within 3 min of standing, and is associated with an increased risk of mortality and cardiovascular events [46]. Heart rate should also be recorded at the time of BP measurements because resting heart rate is an independent predictor of cardiovascular morbid or fatal events [47], although heart rate is not included in any cardiovascular risk algorithm. Table 65.8 summarizes the recommended procedure for routine office BP measurement. It is emphasized that office BP is often performed improperly, with inadequate attention

to the standardized conditions recommended for a valid measurement of office BP. Improper measurement of office BP can lead to inaccurate classification, overestimation of a patient's true BP, and unnecessary treatment.

## UNATTENDED OFFICE BLOOD PRESSURE MEASUREMENT

Automated multiple BP readings in the doctor's office improve the reproducibility of BP measurement, and if the patient is seated alone and unobserved, the 'white-coat effect' (see section 'White-coat hypertension') can be substantially reduced [48] or eliminated [49]. Moreover, the BP values are lower than those obtained by conventional office BP measurement and are similar to, or even less than, those provided by daytime ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM) [50]. Use of unattended office BP measurement in a recent clinical trial [the Systolic Blood Pressure Intervention Trial (SPRINT)] [51] generated controversy about its quantitative relationship to conventional office BP measurement (which has been the basis for all previous epidemiological and clinical trial data); its feasibility in routine clinical practice has also been questioned. Presently, the relationship between BP readings obtained with conventional office BP measurement and unattended office BP measurement remains unclear, but available evidence suggests that conventional office SBP readings may be at least 5–15 mmHg higher than SBP levels obtained by unattended office BP measurements [52]. There is also very limited evidence on the prognostic value of unattended office BP measurements, that is whether they guarantee at least the same ability to predict outcomes as conventional office BP measurements [53].

## OUT-OF-OFFICE BLOOD PRESSURE MEASUREMENT

Out-of-office BP measurement refers to the use of either HBPM or ABPM, the latter usually over 24 h. It provides a larger number of BP measurements than conventional office BP in conditions that are more representative of daily life. Recent position papers and practice guidelines provide comprehensive details for ABPM [54] and HBPM [55], and are briefly summarized below [54,56].

## HOME BLOOD PRESSURE MONITORING

Home BP is the average of all BP readings performed with a semiautomatic, validated BP monitor, for at least 3 days and preferably for 6–7 consecutive days before each clinic visit, with readings in the morning and the evening, taken in a quiet room after 5 min of rest, with the patient seated with their back and arm supported. Two measurements should be taken at each measurement session, performed 1–2 min apart [57].

Compared with office BP, HBPM values are usually lower, and the diagnostic threshold for hypertension is at least 135/85 mmHg (equivalent to office BP at least 140/90 mmHg) (Table 65.9) when considering the average of 3–6 days of home BP values. Compared with office BP, HBPM provides more reproducible BP data and is more

**Table 65.8** Office blood pressure measurement

Patients should be seated comfortably in a quiet environment for 5 min before beginning BP measurements.

Three BP measurements should be recorded, 1–2 min apart, and additional measurements only if the first two readings differ by  $>10$  mmHg. BP is recorded as the average of the last two BP readings.

Additional measurements may have to be performed in patients with unstable BP values due to arrhythmias, such as in patients with AF, in whom manual auscultatory methods should be used as most automated devices have not been validated for BP measurement in patients with AF.<sup>a</sup>

Use a standard bladder cuff (12–13 cm wide and 35 cm long) for most patients, but have larger and smaller cuffs available for larger (arm circumference  $>32$  cm) and thinner arms, respectively.

The cuff should be positioned at the level of the heart, with the back and arm supported to avoid muscle contraction and isometric exercise-dependent increases in BP.

When using auscultatory methods, use phase I and V (sudden reduction/disappearance) Korotkoff sounds to identify SBP and DBP, respectively.

Measure BP in both arms at the first visit to detect possible between-arm differences. Use the arm with the higher value as the reference.

Measure BP 1 min and 3 min after standing from a seated position in all patients at the first measurement to exclude orthostatic hypotension. Lying and standing BP measurements should also be considered in subsequent visits in older people, people with diabetes, and people with other conditions in which orthostatic hypotension may frequently occur.

Record heart rate and use pulse palpation to exclude arrhythmia.

Abbreviations: AF, atrial fibrillation; BP, blood pressure.

<sup>a</sup> Most automatic devices are not validated for BP measurement in patients with AF and will record the highest individual systolic pressure wave form rather than an average of several cardiac cycles. This will lead to overestimation of BP.

**Table 65.9** Definitions of hypertension according to office, ambulatory, and home blood pressure levels

| Category                   | SBP (mmHg) | DBP (mmHg) |
|----------------------------|------------|------------|
| Office BP <sup>a</sup>     | ≥140       | and/or ≥90 |
| Ambulatory BP              |            |            |
| Daytime (or awake) mean    | ≥135       | and/or ≥85 |
| Nighttime (or asleep) mean | ≥120       | and/or ≥70 |
| 24 h mean                  | ≥130       | and/or ≥80 |
| Home BP mean               | ≥135       | and/or ≥85 |

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

<sup>a</sup> Refers to conventional office BP rather than unattended office BP.

closely related to HMOD, particularly LVH [58]. Recent meta-analyses of the few available prospective studies have further indicated that HBPM better predicts cardiovascular morbidity and mortality than office BP [59]. There is also evidence that patient self-monitoring may have a beneficial effect on medication adherence and BP control [60,61], especially when combined with education and counselling [62]. Telemonitoring and smartphone applications may offer additional advantages [63,64], such as an aid to memory to make BP measurements, and as a convenient way to store and review BP data in a digital diary and transmit them. We do not recommend the use of apps as a cuff-independent means of measuring BP.

## AMBULATORY BLOOD PRESSURE MONITORING

ABPM provides the average of BP readings over a defined period, usually 24 h. The device is typically programmed to record BP at 15–30 min intervals, and average BP values are usually provided for daytime, nighttime, and 24 h. A diary of the patient's activities and sleep time can also be recorded. A minimum of 70% usable BP recordings are required for a valid ABPM measurement session. ABPM values are, on average, lower than office BP values, and the diagnostic threshold for hypertension is at least 130/80 mmHg over 24 h, at least 135/85 mmHg for the daytime average, and at least 120/70 for the nighttime average (all equivalent to office BP ≥140/90 mmHg), see Table 65.9.

ABPM is a better predictor of HMOD than office BP [65]. Furthermore, 24 h ambulatory BP mean has been consistently shown to have a closer relationship with morbid or fatal events [66–68], and is a more sensitive risk predictor than office BP of cardiovascular outcomes such as coronary morbid or fatal events and stroke [68–72].

BP normally decreases during sleep. Although the degree of nighttime BP dipping has a normal distribution in a population setting, an arbitrary cut-off has been proposed to define patients as 'dippers' if their nocturnal BP falls by more than 10% of the daytime average BP value; however, the 'dipping' status is often highly variable from day to day and thus is poorly reproducible [73]. Recognized reasons for an absence of nocturnal BP dipping are sleep disturbance, obstructive sleep apnoea, obesity, high salt

intake in salt-sensitive subjects, orthostatic hypotension, autonomic dysfunction, CKD, diabetic neuropathy, and old age [54]. Studies that accounted for daytime and nighttime BP in the same statistical model found that nighttime BP is a stronger predictor of outcomes than daytime BP [54]. The night-to-day ratio is also a significant predictor of outcome, and patients with a reduced nighttime dip in BP (i.e. <10% of the daytime average BP or a night-to-day ratio >0.9) have an increased cardiovascular risk [54]. Moreover, in those in whom there is no nighttime dip in BP or a higher nighttime than daytime average BP, there is a substantially increase in risk [74]. Paradoxically, there is also some evidence of increased risk in patients who have extreme dipping of their nighttime BP [75], although the limited prevalence and reproducibility of this phenomenon makes interpretation of data difficult.

A number of additional indices derived from ABPM recordings have some prognostic value, including 24 h BP variability [76], morning BP surge [77] and the ambulatory arterial stiffness index [78]. However, their incremental predictive value is not yet clear. Thus, these indices should be regarded as research tools, with no current indication for routine clinical use.

## ADVANTAGES AND DISADVANTAGES OF AMBULATORY BLOOD PRESSURE MONITORING AND HOME BLOOD PRESSURE MONITORING

A major advantage of both ABPM and HBPM is that they enable the diagnosis of white-coat and masked hypertension (see section 'White-coat hypertension and masked hypertension'). The relative advantages and disadvantages of HBPM and ABPM are shown in Table 65.10. A particularly important advantage of HBPM is that it is much cheaper and thus more available than ABPM. Another is that it provides multiple measurements over several days or even longer periods, which is clinically relevant because day-to-day BP variability may have an independent prognostic value [79]. Unlike ABPM, typical HBPM devices do not provide BP measurements during routine daily activities and during sleep, although recent technical advances may allow BP during sleep to be measured by HBPM. A further consideration is the potential impact of impaired cognition on the reliability of HBPM measurements and rare instances of obsessional behaviour, circumstances that may favour the use of ABPM if out-of-office BP readings are required. In general, both methods should be regarded as complementary rather than absolute alternatives.

Despite the advances in out-of-office BP measurement over the past 50 years, some fundamental questions remain, the most important of which is whether HBPM-guided or ABPM-guided therapy results in greater reductions in morbidity and mortality than conventional office BP-guided treatment, which has been the diagnostic strategy for all clinical outcome trials.

## WHITE-COAT HYPERTENSION AND MASKED HYPERTENSION

White-coat hypertension refers to the untreated condition in which BP is elevated in the office, but is normal when

**Table 65.10** Comparison of ambulatory blood pressure monitoring and home blood pressure monitoring

| ABPM                                                                                                                                                                                                                                                                                                                                                                                            | HBPM                                                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Advantages</b> <ul style="list-style-type: none"> <li>■ Can identify white-coat and masked hypertension</li> <li>■ Stronger prognostic evidence</li> <li>■ Night-time readings</li> <li>■ Measurement in real-life settings</li> <li>■ Additional prognostic BP phenotypes</li> <li>■ Abundant information from a single measurement session, including short-term BP variability</li> </ul> | <b>Advantages</b> <ul style="list-style-type: none"> <li>■ Can identify white-coat and masked hypertension</li> <li>■ Cheap and widely available</li> <li>■ Measurement in a home setting, which may be more relaxed than the doctor's office</li> <li>■ Patient engagement in BP measurement</li> <li>■ Easily repeated and used over longer periods to assess day-to-day BP variability</li> </ul> |
| <b>Disadvantages</b> <ul style="list-style-type: none"> <li>■ Expensive and sometimes limited availability</li> <li>■ Can be uncomfortable</li> </ul>                                                                                                                                                                                                                                           | <b>Disadvantages</b> <ul style="list-style-type: none"> <li>■ Only static BP is available</li> <li>■ Potential for measurement error</li> <li>■ No nocturnal readings<sup>a</sup></li> </ul>                                                                                                                                                                                                         |

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; HBPM, home blood pressure monitoring.

<sup>a</sup> Techniques are being developed to enable nocturnal BP measurement with home BP devices.

measured by ABPM, HBPM, or both [80]. Conversely, 'masked hypertension' refers to untreated patients in whom the BP is normal in the office, but is elevated when measured by HBPM or ABPM [81]. The term 'true normotension' is used when both office and out-of-office BP measurements are normal, and 'sustained hypertension' is used when both are abnormal. In white-coat hypertension, the difference between the higher office and the lower out-of-office BP is referred to as the 'white-coat effect', and is believed to mainly reflect the pressor response to an alerting reaction elicited by office BP measurements by a doctor or a nurse [82], although other factors are probably also involved [83].

Although the terms white-coat and masked hypertension were originally defined for people who were not being treated for hypertension, they are now also used to describe discrepancies between office and out-of-office BP in patients treated for hypertension, with the terms masked uncontrolled hypertension (MUCH) (office BP controlled but home or ambulatory BP elevated) and white-coat uncontrolled hypertension (WUCH) (office BP elevated but home or ambulatory BP controlled), compared with sustained uncontrolled hypertension (SUCH) [84] (both office and home or ambulatory BP are uncontrolled).

The white-coat effect is used to describe the difference between an elevated office BP (treated or untreated) and a lower home or ambulatory BP in both untreated and treated patients.

## WHITE-COAT HYPERTENSION

Although the prevalence varies between studies, white-coat hypertension can account for up to 30–40% of people (and >50% in the very old) with an elevated office BP. It is more common with increasing age, in women, and in

non-smokers. Its prevalence is lower in patients with HMOD, when office BP is based on repeated measurements, or when a doctor is not involved in the BP measurement. A significant white-coat effect can be seen at all grades of hypertension (including resistant hypertension), but the prevalence of white-coat hypertension is greatest in grade 1 hypertension.

HMOD is less prevalent in white-coat hypertension than in sustained hypertension, and recent studies show that the risk of cardiovascular events associated with white-coat hypertension is also lower than that in sustained hypertension [68,85,86]. Conversely, compared with true normotensives, patients with white-coat hypertension have increased adrenergic activity [87], a greater prevalence of metabolic risk factors, more frequent asymptomatic cardiac and vascular damage, and a greater long-term risk of new-onset diabetes and progression to sustained hypertension and LVH [82]. In addition, although the out-of-office BP values are, by definition, normal in white-coat hypertension, they tend to be higher than those of true normotensive people, which may explain the increased long-term risk of cardiovascular events reported in white-coat hypertension by recent studies after adjustment for demographic and metabolic risk factors [85,86,88–90]. White-coat hypertension has also been shown to have a greater cardiovascular risk in isolated systolic hypertension and older patients [91], and does not appear to be clinically innocent [68]. The diagnosis should be confirmed by repeated office and out-of-office BP measurements, and should include an extensive assessment of risk factors and HMOD. Both ABPM and HBPM are recommended to confirm white-coat hypertension, because the cardiovascular risk appears to be lower (and close to sustained normotension) in those in whom both ABPM and HBPM are both normal [82]; for treatment considerations (see section 'White-coat hypertension').

## MASKED HYPERTENSION

Masked hypertension can be found in approximately 15% of patients with a normal office BP [17]. The prevalence is greater in younger people, men, smokers, and those with higher levels of physical activity, alcohol consumption, anxiety and job stress [54]. Obesity, diabetes, CKD, family history of hypertension, and high-normal office BP are also associated with an increased prevalence of masked hypertension [17]. Masked hypertension is associated with dyslipidaemia and dysglycaemia, HMOD [92], adrenergic activation, and increased risk of developing diabetes and sustained hypertension [81,93]. Meta-analyses and recent studies [68] have shown that the risk of cardiovascular events is substantially greater in masked hypertension compared with normotension, and close to or greater than that of sustained hypertension [68,93–96]. Masked hypertension has also been found to increase the risk of cardiovascular and renal events in diabetes, especially when the BP elevation occurs during the night [95,97].

## SCREENING FOR THE DETECTION OF HYPERTENSION

Hypertension is predominantly an asymptomatic condition that is best detected by structured population screening programmes or opportunistic measurement of BP. When structured population screening programmes have been



undertaken, an alarming number of people (>50%) were unaware they had hypertension [12,98]. This high rate of undetected hypertension occurred irrespective of the income status of the countries studied across the world.

All adults should have their BP recorded in their medical record and be aware of their BP, and further screening should be undertaken at regular intervals with the frequency dependent on the BP level. For healthy people with an optimal office BP (<120/80 mmHg), BP should be remeasured at least every 5 years and more frequently when opportunities arise. In patients with a normal BP (120–129/80–84), BP should be remeasured at least every 3 years. Patients with high-normal BP (130–139/85–89 mmHg) should have their BP recorded annually because of the high rates of progression of high-normal BP to hypertension. This is true also for people in whom masked hypertension is detected.

## CONFIRMING THE DIAGNOSIS OF HYPERTENSION

BP can be highly variable, thus the diagnosis of hypertension should not be based on a single set of BP readings at a single office visit, unless the BP is substantially increased (e.g. grade 3 hypertension) and there is clear evidence of HMOD (e.g. hypertensive retinopathy with exudates and haemorrhages, or LVH, or vascular or renal damage). For all others (i.e. almost all patients), repeat BP measurements at repeat office visits have been a long-standing strategy to confirm a persistent elevation in BP, as well as for the classification of the hypertension status in clinical practice and RCTs. The number of visits and the time interval between visits varies according to the severity of the hypertension, and is inversely related to the severity of hypertension. Thus, more substantial BP elevation (e.g. grade 2 or more) requires fewer visits and shorter time intervals between visits (i.e. a few days or

weeks), depending on the severity of BP elevation and whether there is evidence of CVD or HMOD. Conversely, in patients with BP elevation in the grade 1 range, the period of repeat measurements may extend over a few months, especially when the patient is at low risk and there is no HMOD. During this period of BP assessment, cardiovascular risk assessment and routine screening tests are usually performed (see section 'Definition, classification, and epidemiological aspects of hypertension').

These Guidelines also support the use of out-of-office BP measurements (i.e. HBPM and/or ABPM) as an alternative strategy to repeated office BP measurements to confirm the diagnosis of hypertension, when these measurements are logistically and economically feasible (Figure 65.2) [99]. This approach can provide important supplementary clinical information, for example detecting white-coat hypertension (see section 'White-coat hypertension'), which should be suspected, especially in people with grade 1 hypertension on office BP measurement and in whom there is no evidence of HMOD or CVD [100] (Table 65.11). A particular challenge is the detection of masked hypertension (see section 'Masked hypertension'). Masked hypertension is more likely in people with a BP in the high-normal range in whom out-of-office BP should be considered to exclude masked hypertension (see Table 65.8). Out-of-office BP measurements are also indicated in specific circumstances (see section 'Clinical indications for out-of-office blood pressure measurements' and Table 65.11).

## CLINICAL INDICATIONS FOR OUT-OF-OFFICE BLOOD PRESSURE MEASUREMENTS

Out-of-office BP measurements are increasingly used, especially HBPM but also ABPM, to confirm the diagnosis of hypertension. Out-of-office BP measurement provides important complementary information, as discussed above. The clinical indications for out-of-office

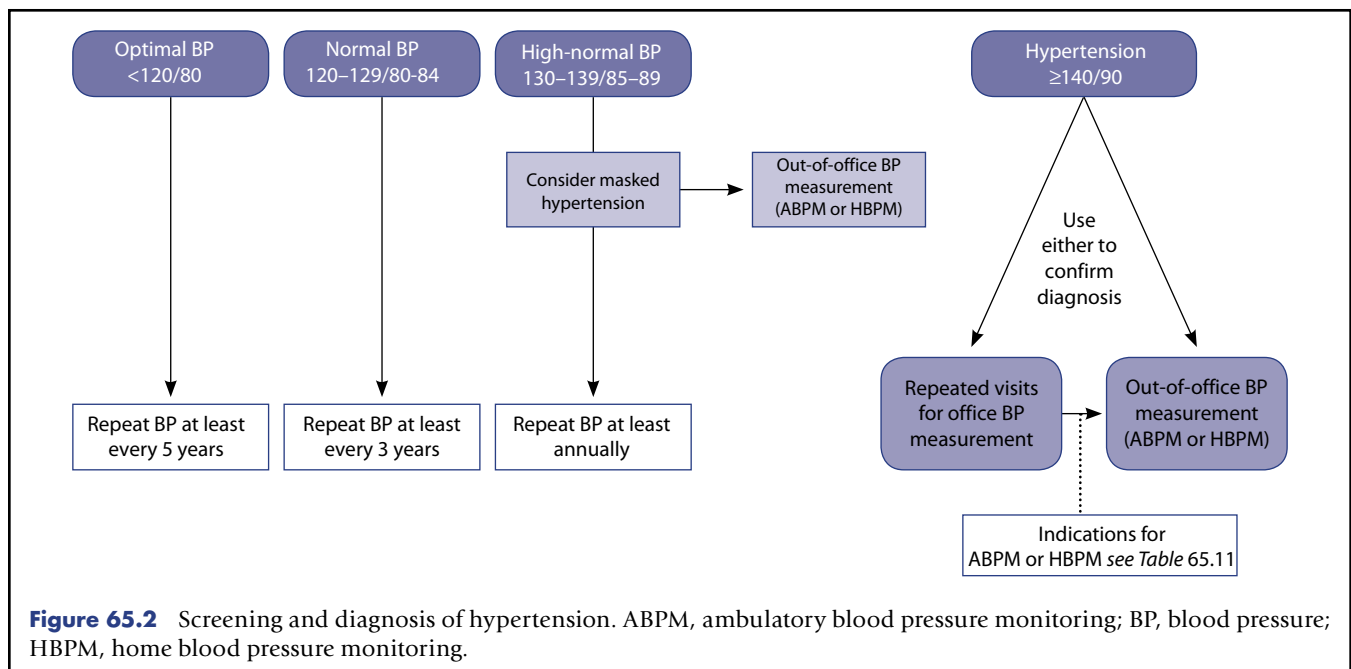


**Figure 65.2** Screening and diagnosis of hypertension. ABPM, ambulatory blood pressure monitoring; BP, blood pressure; HBPM, home blood pressure monitoring.



**Table 65.11** Clinical indications for home blood pressure monitoring or ambulatory blood pressure monitoring

|                                                                                                                                                                                                                                                                                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Conditions in which white-coat hypertension is more common, for example: <ul style="list-style-type: none"> <li>■ Grade I hypertension on office BP measurement</li> <li>■ Marked office BP elevation without HMOD</li> </ul>                                                                 |
| Conditions in which masked hypertension is more common, for example: <ul style="list-style-type: none"> <li>■ High-normal office BP</li> <li>■ Normal office BP in individuals with HMOD or at high total cardiovascular risk</li> </ul>                                                      |
| Postural and postprandial hypotension in untreated and treated patients                                                                                                                                                                                                                       |
| Evaluation of resistant hypertension                                                                                                                                                                                                                                                          |
| Evaluation of BP control, especially in treated higher-risk patients                                                                                                                                                                                                                          |
| Exaggerated BP response to exercise                                                                                                                                                                                                                                                           |
| When there is considerable variability in the office BP                                                                                                                                                                                                                                       |
| Evaluating symptoms consistent with hypotension during treatment                                                                                                                                                                                                                              |
| Specific indications for ABPM rather than HBPM: <ul style="list-style-type: none"> <li>■ Assessment of nocturnal BP values and dipping status (e.g. suspicion of nocturnal hypertension, such as in sleep apnoea, CKD, diabetes, endocrine hypertension, or autonomic dysfunction)</li> </ul> |

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CKD, chronic kidney disease; HBPM, home blood pressure monitoring; HMOD, hypertension-mediated organ damage.

BP measurements are shown in Table 65.11. HBPM is also increasingly used by patients to monitor their BP control, which increases their engagement and may improve their adherence to treatment and BP control [61,101,102]. It is likely that, with increased availability and lower cost of these devices, this will become more commonplace.

## BLOOD PRESSURE DURING EXERCISE AND AT HIGH ALTITUDE

It is important to recognize that BP increases during dynamic and static exercise, and that the increase is more pronounced for SBP than for DBP [103], although only SBP can be measured reliably with noninvasive methods. There is currently no consensus on normal BP response during exercise. The increase in SBP during exercise is related to preexercise resting BP, age, arterial stiffness and abdominal obesity, and is somewhat greater in women than in men and in unfit individuals. There is some evidence that an excessive rise in BP during exercise predicts the development of hypertension, independently from BP at rest [104]. Nevertheless, exercise testing is not recommended as part of the routine evaluation of hypertension because of various limitations, including a lack of standardization of methodology and definitions. Importantly, except in the presence of very high BP values (grade 3 hypertension), patients or athletes, with treated or untreated hypertension should not be discouraged from regular exercise, especially aerobic

exercise, which is considered beneficial as part of lifestyle changes to reduce BP (see section 'Lifestyle changes').

Evidence is available that BP increases with high altitude exposure, especially above 3000 m and possibly above 2000 m [105]. This is due to a number of factors including sympathetic activation. Patients with grade 2 hypertension and increased cardiovascular risk should check their BP values before and during high altitude (>2500 m) exposure. Patients with grade 1 hypertension may reach very high altitude (>4000 m) with adequate medical therapy; uncontrolled severe hypertensive patients (grade 3) should avoid exposure to very high altitude [105].

## CENTRAL AORTIC PRESSURE

Various techniques allow aortic BP (central BP) to be derived from peripheral BP measurements using dedicated algorithms [106,107]. Some studies and meta-analyses have shown that in hypertensive patients, central BP predicts cardiovascular events and that there is a differential effect of antihypertensive drugs on central compared with brachial BP [108]. The incremental prognostic value of central vs. conventional clinic BP measurement remains unclear [109]. An exception may be isolated systolic hypertension in the young, in whom peripheral BP may be disproportionately elevated relative to a normal central BP. This occurs in a small fraction of younger people, mainly men with isolated systolic hypertension, and it remains unclear whether such patients are at lower risk than suggested by their brachial office BP [110,111].

| BP measurement                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                    |                    |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Recommendations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Class <sup>a</sup> | Level <sup>b</sup> |
| Screening programmes for hypertension are recommended. All adults (18 years or older) should have their office BP measured and recorded in their medical file, and be aware of their BP [12,98].                                                                                                                                                                                                                                                                                                           | <b>I</b>           | <b>B</b>           |
| <ul style="list-style-type: none"> <li>■ Further BP recording is indicated, at least every 5 years if BP remains optimal.</li> <li>■ Further BP recording is indicated, at least every 3 years if BP remains normal.</li> <li>■ If BP remains high-normal, further BP recording, at least annually, is recommended.</li> <li>■ In older patients (&gt;50 years), more frequent screening of office BP should be considered for each BP category because of the steeper rise in SBP with ageing.</li> </ul> | <b>I</b>           | <b>C</b>           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <b>I</b>           | <b>C</b>           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <b>I</b>           | <b>C</b>           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <b>Ila</b>         | <b>C</b>           |
| It is recommended that office BP should be measured in both arms at least at the first visit because a between-arm SBP difference of >15 mmHg is suggestive of atheromatous disease and is associated with an increased CV risk [45].                                                                                                                                                                                                                                                                      | <b>I</b>           | <b>A</b>           |
| If a between-arm difference in BP is recorded, then it is recommended that all subsequent BP readings use the arm with the higher BP reading.                                                                                                                                                                                                                                                                                                                                                              | <b>I</b>           | <b>C</b>           |

Continued

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |            |          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|----------|
| It is recommended that the diagnosis of hypertension should be based on:<br>■ Repeated office BP measurements on more than one visit, except when hypertension is severe (e.g. grade 3 and especially in high-risk patients). At each visit, three BP measurements should be recorded, 1–2 min apart, and additional measurements should be performed if the first two readings differ by >10 mmHg. The patient's BP is the average of the last two BP readings. | <b>I</b>   | <b>C</b> |
| Or<br>■ Out-of-office BP measurement with ABPM and/or HBPM, provided that these measurements are logistically and economically feasible.                                                                                                                                                                                                                                                                                                                         | <b>I</b>   | <b>C</b> |
| Out-of-office BP (i.e. ABPM or HBPM) is specifically recommended for a number of clinical indications, such as identifying white-coat and masked hypertension, quantifying the effects of treatment, and identifying possible causes of side effects [17,54,62,68,72] (e.g. symptomatic hypotension).                                                                                                                                                            | <b>I</b>   | <b>A</b> |
| It is recommended that all hypertensive patients undergo pulse palpation at rest to determine heart rate and search for arrhythmias such as AF [20,47].                                                                                                                                                                                                                                                                                                          | <b>I</b>   | <b>C</b> |
| Other BP measures and indices (pulse pressure, BP variability, exercise BP, and central BP) may be considered but are not often used for routine clinical use at present.<br>They may provide useful additional information in some circumstances and are valuable tools for research.                                                                                                                                                                           | <b>IIb</b> | <b>C</b> |

Abbreviations: ABPM, ambulatory blood pressure monitoring; AF, atrial fibrillation; BP, blood pressure; HBPM, home blood pressure monitoring.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

## CLINICAL EVALUATION AND ASSESSMENT OF HYPERTENSION-MEDIATED ORGAN DAMAGE IN PATIENTS WITH HYPERTENSION

### CLINICAL EVALUATION

The purpose of the clinical evaluation is to establish the diagnosis and grade of hypertension, screen for potential secondary causes of hypertension, identify factors potentially contributing to the development of hypertension (lifestyle, concomitant medications or family history); identify concomitant cardiovascular risk factors (including lifestyle and family history); identify concomitant diseases and establish whether there is evidence of HMOD or existing cardiovascular, cerebrovascular or renal disease.

### MEDICAL HISTORY

A thorough medical history (Table 65.12) should address in particular:

1. Time of the first diagnosis of hypertension, including records of any previous medical screening, hospitalization, etc.
2. Record any current and past BP values
3. Record current and past antihypertensive medications
4. Record other medications
5. Family history of hypertension, CVD, stroke, or renal disease
6. Lifestyle evaluation, including exercise levels, body weight changes, diet history, smoking history, alcohol use, recreational drug use, sleep history and impact of any treatments on sexual function
7. History of any concomitant cardiovascular risk factors
8. Details and symptoms of past and present comorbidities
9. Specific history of potential secondary causes of hypertension (see section 'Secondary hypertension')
10. History of past pregnancies and oral contraceptive use
11. History of menopause and hormone replacement therapy
12. Use of liquorice
13. Use of drugs that may have a pressor effect

### PHYSICAL EXAMINATION AND CLINICAL INVESTIGATIONS

Physical examination provides important indications of potential causes of secondary hypertension, signs of comorbidities, and HMOD. Office BP and heart rate should be measured as summarized in section 'Blood pressure measurement'.

Measurements of office BP on more than one occasion are usually required to confirm the diagnosis of hypertension unless HBPM or ABPM is used to confirm the diagnosis (see section 'Blood pressure measurement').

Details of the requirements for a comprehensive clinical examination are outlined in Table 65.13, and this should be adapted according to the severity of hypertension and clinical circumstances. Suggested routine clinical investigations are outlined in Table 65.14.

### ASSESSMENT OF HYPERTENSION-MEDIATED ORGAN DAMAGE

HMOD refers to structural or functional changes in arteries or end organs (heart, blood vessels, brain, eyes, and kidney) caused by an elevated BP, and is a marker of pre-clinical or asymptomatic CVD [112]. HMOD is common in severe or long-standing hypertension, but can also be found in less severe hypertension. With wider use of imaging, HMOD is becoming increasingly apparent in asymptomatic patients [43]. Cardiovascular risk increases with the presence of HMOD, and more so when damage affects multiple organs [16,113,114]. Some types of HMOD can be reversed by antihypertensive treatment, especially when used early, but with long-standing hypertension, HMOD may become irreversible despite improved BP control [115,116]. Nevertheless, BP-lowering treatment is still important as it may delay the further progression of HMOD and will reduce the elevated cardiovascular risk of these patients [116]. Although poor technical provision and cost may limit the search for HMOD in some countries,

**Table 65.12** Key information to be collected in personal and family medical history**Risk factors**

- Family and personal history of hypertension, CVD, stroke, or renal disease
- Family and personal history of associated risk factors (e.g. familial hypercholesterolaemia)
- Smoking history
- Dietary history and salt intake
- Alcohol consumption
- Lack of physical exercise/sedentary lifestyle
- History of erectile dysfunction
- Sleep history, snoring, sleep apnoea (information also from partner)
- Previous hypertension in pregnancy/pre-eclampsia

**History and symptoms of HMOD, CVD, stroke, and renal disease**

- Brain and eyes: headache, vertigo, syncope, impaired vision, TIA, sensory or motor deficit, stroke, carotid revascularization, cognitive impairment, dementia (in the elderly)
- Heart: chest pain, shortness of breath, oedema, myocardial infarction, coronary revascularization, syncope, history of palpitations, arrhythmias (especially AF), heart failure
- Kidney: thirst, polyuria, nocturia, haematuria, urinary tract infections
- Peripheral arteries: cold extremities, intermittent claudication, pain-free walking distance, pain at rest, peripheral revascularization
- Patient or family history of CKD (e.g. polycystic kidney disease)

**History of possible secondary hypertension**

- Young onset of grade 2 or 3 hypertension (<40 years), or sudden development of hypertension or rapidly worsening BP in older patients
- History of renal/urinary tract disease
- Recreational drug/substance abuse/concurrent therapies: corticosteroids, nasal vasoconstrictor, chemotherapy, yohimbine, liquorice
- Repetitive episodes of sweating, headache, anxiety, or palpitations, suggestive of Pheochromocytoma
- History of spontaneous or diuretic-provoked hypokalaemia, episodes of muscle weakness, and tetany (hyperaldosteronism)
- Symptoms suggestive of thyroid disease or hyperparathyroidism
- History of or current pregnancy and oral contraceptive use
- History of sleep apnoea

**Antihypertensive Drug Treatment**

- Current/past antihypertensive medication including effectiveness and intolerance to previous medications
- Adherence to therapy

Abbreviations: AF, atrial fibrillation; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; HMOD, hypertension-mediated organ damage; TIA, transient ischaemic attack.

**Table 65.13** Key steps in physical examination**Body habitus**

- Weight and height measured on a calibrated scale, with calculation of BMI
- Waist circumference

**Signs of HMOD**

- Neurological examination and cognitive status
- Fundoscopic examination for hypertensive retinopathy
- Palpation and auscultation of heart and carotid arteries
- Palpation of peripheral arteries
- Comparison of BP in both arms (at least once)

**Secondary hypertension**

- Skin inspection: café-au-lait patches of neurofibromatosis (pheochromocytoma)
- Kidney palpation for signs of renal enlargement in polycystic kidney disease
- Auscultation of heart and renal arteries for murmurs or bruits indicative of aortic coarctation, or renovascular hypertension
- Comparison of radial with femoral pulse: to detect radio-femoral delay in aortic coarctation
- Signs of Cushing's disease or acromegaly
- Signs of thyroid disease

Abbreviations: BMI, body mass index; BP, blood pressure; HMOD, hypertension-mediated organ damage.

**Table 65.14** Routine workup for evaluation of hypertensive patients**Routine laboratory tests**

Haemoglobin and/or haematocrit

Fasting blood glucose and glycated HbA<sub>1c</sub>

Blood lipids: total cholesterol, LDL cholesterol, HDL cholesterol

Blood triglycerides

Blood potassium and sodium

Blood uric acid

Blood creatinine and eGFR

Blood liver function tests

Urine analysis: microscopic examination; urinary protein by dipstick test or, ideally, albumin:creatinine ratio

12-lead ECG

Abbreviations: eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, haemoglobin A1c.

**Table 65.15** Assessment of hypertension-mediated organ damage

| Basic screening tests for HMOD           | Indication and interpretation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 12-lead ECG                              | Screen for LVH and other possible cardiac abnormalities, and to document heart rate and cardiac rhythm                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Urine albumin:creatinine ratio           | To detect elevations in albumin excretion indicative of possible renal disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Blood creatinine and eGFR                | To detect possible renal disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Fundoscopy                               | To detect hypertensive retinopathy, especially in patients with grade 2 or 3 hypertension                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| More detailed screening for HMOD         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Echocardiography                         | To evaluate cardiac structure and function, when this information will influence treatment decisions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Carotid ultrasound                       | To determine the presence of carotid plaque or stenosis, particularly in patients with cerebrovascular disease or vascular disease elsewhere                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Abdominal ultrasound and Doppler studies | To evaluate renal size and structure (e.g. scarring) and exclude renal tract obstruction as possible underlying causes of CKD and hypertension<br>Evaluate abdominal aorta for evidence of aneurysmal dilatation and vascular disease<br>Examine adrenal glands for evidence of adenoma or pheochromocytoma (CT or MRI preferred for detailed examination); see section 'Secondary hypertension' regarding screening for secondary hypertension<br>Renal artery Doppler studies to screen for the presence of renovascular disease, especially in the presence of asymmetric renal size |
| PWV                                      | An index of aortic stiffness and underlying arteriosclerosis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| ABI                                      | Screen for evidence of LEAD                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Cognitive function testing               | To evaluate cognition in patients with symptoms suggestive of cognitive impairment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Brain imaging                            | To evaluate the presence of ischaemic or haemorrhagic brain injury, especially in patients with a history of cerebrovascular disease or cognitive decline                                                                                                                                                                                                                                                                                                                                                                                                                               |

Abbreviations: ABI, ankle-brachial index; CKD, chronic kidney disease; CT, computed tomography; eGFR, estimated glomerular filtration rate; HMOD, hypertension-mediated organ damage; LEAD, lower extremity artery disease; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; PWV, pulse wave velocity.

it is recommended that basic screening for HMOD is performed in all hypertensive patients and more detailed assessment is performed when the presence of HMOD might influence treatment decisions. The various investigations to establish HMOD are shown in [Table 65.15](#).

### USING HYPERTENSION-MEDIATED ORGAN DAMAGE TO HELP STRATIFY RISK IN HYPERTENSIVE PATIENTS

As discussed in section 'Definition, classification, and epidemiological aspects of hypertension', hypertensive patients with documented CVD, diabetes, CKD, grade 3 hypertension, or marked cholesterol elevation (e.g. familial hypercholesterolaemia) are already at high or very high cardiovascular risk (10% risk of a fatal event). Thus, the presence of HMOD is unlikely to influence treatment, as these patients should already receive lifestyle interventions, BP-lowering medications, statins, and in some cases antiplatelet therapy, to reduce their risk [35] (see section 'Managing concomitant cardiovascular disease risk').

The main advantage of detecting HMOD is that it may reclassify a patient's SCORE risk assessment from low to moderate or from moderate to high risk [117]. The specific impact of HMOD [114] with regard to the reclassification of risk estimation according to the SCORE system has not been clearly defined. The SCORE system already takes account of the grade of hypertension as SBP is included in the risk calculation. Moreover, CKD and the presence of vascular disease on imaging are already specified as high or very high risk ([Table 65.5](#)). Conditioning of the risk score by the presence of HMOD will be most important in middle-aged patients with hypertension, many of

whom will be at moderate-risk and at higher risk if HMOD is detected. Moreover, a risk-conditioning effect of HMOD will also be important in younger hypertensive patients who are invariably classified as low risk according to the SCORE system. In addition, detecting HMOD in younger patients with grade 1 hypertension provides unequivocal evidence of hypertension-mediated damage and indicates a clear need for BP-lowering treatment in patients who may be reluctant to be treated. For the same reason, the presence of HMOD in a patient with high-normal BP would also provide a rationale to consider BP-lowering treatment.

Another important consideration is whether the presence of a specific manifestation of HMOD (e.g. LVH or CKD) might influence the selection of drug treatment for hypertension. This was considered important in the previous guidelines [17], but is now considered less important. In patients more likely to have HMOD (i.e. those with high grade 1 or grade 2–3 hypertension), we now recommend initial treatment with a combination of two drugs, usually an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) in combination with a calcium channel blocker (CCB) or thiazide-type diuretic, which would be the optimal treatment for all manifestations of HMOD (see section 'Treatment of hypertension').

## CHARACTERISTICS OF HYPERTENSION-MEDIATED ORGAN DAMAGE

### THE HEART IN HYPERTENSION

Chronically increased left ventricular workload in hypertensive patients can result in LVH, impaired left ventricular



relaxation, left atrial enlargement, an increased risk of arrhythmias, especially AF, and an increased risk of heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF).

### ELECTROCARDIOGRAM

A 12-lead ECG should be part of the routine assessment in all hypertensive patients. The ECG is not a particularly sensitive method of detecting LVH and its sensitivity varies according to body weight. ECG LVH provides independent prognostic information, even after adjusting for other cardiovascular risk factors and echocardiographic left ventricular mass [118]. In addition to LVH, the presence of a 'strain pattern' on an ECG is associated with increased risk [119]. The prevalence of ECG LVH increases with the severity of hypertension [120]. The most commonly used criteria to define ECG LVH are shown in Table 65.16.

The ECG cannot exclude LVH because it has poor sensitivity. When detailed information on cardiac structure and function will influence treatment decisions, echocardiography is recommended. When LVH is present on the ECG, it can be used to detect changes in LVH during follow-up in untreated and treated patients [121,122].

### TRANSTHORACIC ECHOCARDIOGRAPHY IN HYPERTENSION

Echocardiographic LVH is a potent predictor of mortality in both hypertensive patients and the general population [123,124], and regression of echocardiographic LVH due to treatment of hypertension predicts an improved prognosis [125]. Two-dimensional transthoracic echocardiography (TTE) also provides information about left ventricular geometry, left atrial volume, aortic root dimensions, left ventricular systolic and diastolic function, pump performance, and output impedance [123,126,127]. Whether additional parameters other than evidence of increased left ventricular mass and left atrial dilatation are useful to help stratify cardiovascular risk is uncertain [123,126,128]. The partition values recommended for the definition of LVH by echocardiography are shown in Table 65.17.

Three-dimensional TTE is a more reliable method for quantitative analysis [129], specifically for left ventricular mass [130], volumes, and ejection fraction, and has superior reproducibility to two-dimensional TTE but much less prognostic validation [131]. More detailed information on the use of echocardiography to assess the hypertensive

**Table 65.16** The most commonly used simple criteria and recognized cut-off points for definitions of electrocardiogram left ventricular hypertrophy

| ECG voltage criteria                            | Criteria for LVH               |
|-------------------------------------------------|--------------------------------|
| $S_{V1}+R_{V5}$ (Sokolow–Lyon criterion)        | >35 mm                         |
| R wave in aVL                                   | ≥11 mm                         |
| $S_{V3}+R_{aVL}$ (Cornell voltage) <sup>a</sup> | >28 mm (men)<br>>20 mm (women) |
| Cornell duration product <sup>b</sup>           | >2440 mm*ms                    |

Abbreviation: LVH, left ventricular hypertrophy.

<sup>a</sup> Sum of limb and precordial lead voltage.

<sup>b</sup> Product of Cornell voltage×QRS duration (mm\*ms).

**Table 65.17** Echocardiographic definitions of left ventricular hypertrophy, concentric geometry, left ventricular chamber size, and left atrial dilatation

| Parameter                            | Measure                                                           | Abnormality threshold        |
|--------------------------------------|-------------------------------------------------------------------|------------------------------|
| LVH                                  | Left ventricular mass/height <sup>2.7</sup> (g/m <sup>2.7</sup> ) | >50 (men)<br>>47 (women)     |
| LVH <sup>a</sup>                     | Left ventricular mass/BSA (g/m <sup>2</sup> )                     | >115 (men)<br>>95 (women)    |
| Left ventricular concentric geometry | RWT                                                               | ≥0.43                        |
| Left ventricular chamber size        | Left ventricular end-diastolic diameter/height (cm/m)             | >3.4 (men)<br>>3.3 (women)   |
| Left atrial size (elliptical)        | Left atrial volume/height <sup>2</sup> (mL/m <sup>2</sup> )       | >18.5 (men)<br>>16.5 (women) |

Abbreviations: BSA, body surface area; LVH, left ventricular hypertrophy; RWT, relative wall thickness.

<sup>a</sup> BSA normalization may be used in normal weight patients.

heart is available [43]. Cardiac magnetic resonance is the gold standard for cardiac anatomical and functional quantification [132–134].

Abnormal left ventricular geometry in hypertensive patients is frequently associated with diastolic dysfunction [127,135], which can be further evaluated by a combination of transmitral flow and tissue Doppler studies [136]. Left atrial size is also frequently increased in hypertensive patients and is associated with adverse cardiovascular events [128,137] and incident AF [138], and is related to diastolic dysfunction [139,140]. During the diagnostic workup for secondary hypertension, a suprasternal view should also be performed for the identification of aortic coarctation [141].

### THE BLOOD VESSELS IN HYPERTENSION

#### CAROTID ARTERY

Carotid intima–media thickness (IMT) quantified by carotid ultrasound, and/or the presence of plaques, predicts cardiovascular risk [42,142]. This holds true both for the IMT value at the carotid bifurcations (reflecting primarily atherosclerosis) and for the IMT value at the level of the common carotid artery (reflecting primarily hypertension-related hypertrophy). A carotid IMT more than 0.9 mm is considered abnormal [143], but the upper limit of normality varies with age. The presence of a plaque can be identified by an IMT at least 1.5 mm, or by a focal increase in thickness of 0.5 mm or 50% of the surrounding carotid IMT value [144]. Stenotic carotid plaques have a strong predictive value for both stroke and myocardial infarction, independent of traditional cardiovascular risk factors [42,142], and confer superior prognostic accuracy for future myocardial infarction compared with IMT [145]. The presence of carotid plaques will automatically reclassify patients from intermediate to high risk [146,147]; however, routine carotid imaging is not recommended unless clinically indicated (i.e. presence of carotid bruit, previous transient ischaemic attack (TIA) or cerebrovascular disease, or as part of the assessment of patients with evidence of vascular disease).



### PULSE WAVE VELOCITY

Large artery stiffening is the most important pathophysiological determinant of isolated systolic hypertension and age-dependent increase in pulse pressure [148]. Carotid-femoral pulse wave velocity (PWV) is the gold standard for measuring large artery stiffness [149]. Reference values for PWV are available in healthy populations and patients at increased cardiovascular risk [150]. A PWV more than 10 m/s is considered a conservative estimate of significant alterations of aortic function in middle-aged hypertensive patients [149]. The additive value of PWV above and beyond traditional risk factors, including SCORE and the Framingham risk score, has been suggested by several studies [151]. However, routine use of PWV measurement is not practical and is not recommended for routine practice.

### ANKLE-BRACHIAL INDEX

Ankle-brachial index (ABI) may be measured either with automated devices, or with a continuous wave Doppler unit and a BP sphygmomanometer. A low ABI (i.e. <0.9) indicates lower extremity artery disease (LEAD), is usually indicative of advanced atherosclerosis [152], and has predictive value for cardiovascular events [153], being associated with an almost two-fold greater 10-year cardiovascular mortality and major coronary event rate, compared with the overall rate in each Framingham category [153]. Even asymptomatic LEAD, detected by a low ABI, is associated in men with a high incidence of cardiovascular morbid and fatal events, approaching 20% in 10 years [153,154]. Routine use of ABI is not recommended in hypertensive patients, but should be considered in patients with symptoms or signs of LEAD, or in moderate-risk patients in whom a positive test would reclassify the patient as high-risk.

### THE KIDNEY IN HYPERTENSION

Hypertension is the second most important cause of CKD after diabetes. Hypertension may also be the presenting feature of asymptomatic primary renal disease. An alteration of renal function is most commonly detected by an increase in serum creatinine. This is an insensitive marker of renal impairment because a major reduction in renal function is needed before serum creatinine rises. Furthermore, BP reduction by antihypertensive treatment often leads to an acute increase in serum creatinine by as much as 20–30%, especially with renin-angiotensin system (RAS) blockers, which has a functional basis and does not usually reflect manifest renal injury, but the long-term clinical significance is unclear [155,156]. The diagnosis of hypertension-induced renal damage is based on the finding of reduced renal function and/or the detection of albuminuria. CKD is classified according to estimated glomerular filtration rate (eGFR), calculated by the 2009 CKD-Epidemiology Collaboration formula [157].

The albumin:creatinine ratio (ACR) is measured from a spot urine sample (preferably early morning urine), and is the preferred method to quantify urinary albumin excretion. A progressive reduction in eGFR and increased albuminuria indicate progressive loss of renal function, and are both independent and additive predictors of increased cardiovascular risk and progression of renal disease [158].

Serum creatinine, eGFR and ACR should be documented in all hypertensive patients, and if CKD is diagnosed, repeated at least annually [159]. One negative urinary dipstick test does not rule out albuminuria, in contrast to a normal ACR [160].

### HYPERTENSIVE RETINOPATHY

The prognostic significance of hypertensive retinopathy by fundoscopy has been well documented [161]. Detection of retinal haemorrhages, microaneurysms, hard exudates, cotton wool spots, and papilloedema is highly reproducible, indicates severe hypertensive retinopathy, and is highly predictive of mortality [161,162]. In contrast, evidence of arteriolar narrowing, either focal or general, and arteriovenous nicking at early stages of hypertensive retinopathy have less predictive value [163], and limited interobserver and intraobserver reproducibility, even with experienced observers [164]. Fundoscopy should be performed in patients with grade 2 or 3 hypertension or hypertensive patients with diabetes, in whom significant retinopathy is more likely. Fundoscopy may be considered in other hypertensive patients. The increasing emergence of new techniques to visualize the fundus through smartphone technologies should increase the feasibility of more routine fundoscopy [165].

### THE BRAIN IN HYPERTENSION

Hypertension increases the prevalence of brain damage, of which transient ischaemic attack (TIA) and stroke are the most dramatic acute clinical manifestations. In the asymptomatic phase, brain damage can be detected by MRI as white matter hyperintensities, silent microinfarcts, (most of which are small and deep, i.e. lacunar infarctions), microbleeds and brain atrophy [166,167]. White matter hyperintensities and silent infarcts are associated with an increased risk of stroke and cognitive decline due to degenerative and vascular dementia [166–169]. Availability and cost do not permit the widespread use of brain MRI for the evaluation of hypertensive patients, but white matter hyperintensity and silent brain infarcts should be sought in all hypertensive patients with neurological disturbances, cognitive decline, and, particularly, memory loss [168,169]. A family history of cerebral haemorrhage at middle age and early-onset dementia should prompt MRI. Cognitive impairment in older patients is, at least in part, hypertension-related, and cognitive evaluation tests should be considered in the clinical assessment of hypertensive patients with a history suggestive of early cognitive impairment. The Mini-Mental State Examination has been the most widely used method in clinical trials, but is now being superseded by more sophisticated cognitive tests that are more suitable for routine clinic visits [170].

### HYPERTENSION-MEDIATED ORGAN DAMAGE REGRESSION AND CARDIOVASCULAR RISK REDUCTION WITH ANTIHYPERTENSIVE TREATMENT

As discussed above, HMOD assessment may play a role in stratifying the risk of patients with hypertension. In posthoc

**Table 65.18** Sensitivity to detect treatment-induced changes, reproducibility and operator independence, time to changes, and prognostic value of changes provided by markers of hypertension-mediated organ damage

| Marker of HMOD            | Sensitivity to changes | Reproducibility and operator independence | Time to changes        | Prognostic value of the change |
|---------------------------|------------------------|-------------------------------------------|------------------------|--------------------------------|
| LVH by ECG                | Low                    | High                                      | Moderate (>6 months)   | Yes                            |
| LVH by echocardiogram     | Moderate               | Moderate                                  | Moderate (>6 months)   | Yes                            |
| LVH by CMR                | High                   | High                                      | Moderate (>6 months)   | No data                        |
| eGFR                      | Moderate               | High                                      | Very slow (years)      | Yes                            |
| Urinary protein excretion | High                   | Moderate                                  | Fast (weeks to months) | Moderate                       |
| Carotid IMT               | Very low               | Low                                       | Slow (>12 months)      | No                             |
| PWV                       | High                   | Low                                       | Fast (weeks to months) | Limited data                   |
| Ankle-brachial index      | Low                    | Moderate                                  | Slow (>12 months)      | Moderate                       |

Abbreviations: CMR, cardiac magnetic resonance; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HMOD, hypertension-mediated organ damage; IMT, intima-media thickness; LVH, left ventricular hypertrophy; PWV, pulse wave velocity.

analyses, BP treatment-induced regression of some (but not all) manifestations of asymptomatic HMOD, as a consequence of treatment, is associated with a reduction in cardiovascular risk, thereby providing additional information on the effectiveness of treatment in individual patients [16,104,171]. This has been best illustrated for the treatment-induced regression of LVH measured by either ECG or echocardiography [125,172,173]. A reduced incidence of cardiovascular events and slower progression of renal disease has been reported with a treatment-induced reduction in urinary protein excretion in both diabetic and nondiabetic patients, especially for microalbuminuria [174], but results are discordant [175–179]. There is also evidence that treatment-induced changes in eGFR predict cardiovascular events [180] and progression to end-stage renal disease [181,182]. Two meta-analyses [183,184] failed to document any predictive value of treatment-induced reductions in carotid IMT for cardiovascular events. Evidence on the predictive power of treatment-induced changes on other measures of HMOD (PWV and ABI) are either limited or absent. Regression of HMOD might not be possible even when BP is controlled, particularly when HMOD is advanced, because some of the changes become irreversible.

The information available on the sensitivity and timing of changes in HMOD during antihypertensive treatment is summarized in Table 65.18. If, when, and how often the assessment of HMOD should be performed has not been validated in follow-up studies. HMOD can also develop during the course of antihypertensive treatment [185], and this may be accompanied by increased risk [186–188].

## WHEN TO REFER A PATIENT WITH HYPERTENSION FOR HOSPITAL-BASED CARE

Hypertension is a very common condition and most patients with hypertension, in most healthcare systems, will be managed in the primary care setting. However, there are circumstances in which a referral for routine hospital-based evaluation and treatment may be required, keeping in mind that in some instances out-of-office or office-based care of hypertensive patients depends on the healthcare organization of a given country:

1. Patients in whom secondary hypertension is suspected (see section 'Secondary hypertension')
2. Younger patients (<40 years) with grade 2 or more severe hypertension in whom secondary hypertension should be excluded
3. Patients with treatment-resistant hypertension (see section 'Resistant hypertension')
4. Patients in whom more detailed assessment of HMOD would influence treatment decisions
5. Patients with sudden onset of hypertension when BP has previously been normal
6. Other clinical circumstances in which the referring doctor feels more specialist evaluation is required.

There are also rarer circumstances in which a patient with hypertension should be referred to hospital for emergency care, which will often require inpatient care (see section 'Hypertension urgencies and emergencies').

## Clinical evaluation and HMOD assessment

| Recommendations                                                                                                             | Class <sup>a</sup> | Level <sup>b</sup> |
|-----------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| <b>Heart</b>                                                                                                                |                    |                    |
| 12-lead ECG is recommended for all hypertensive patients [120].                                                             | I                  | B                  |
| Echocardiography:                                                                                                           |                    |                    |
| ■ Is recommended in hypertensive patients when there are ECG abnormalities or signs or symptoms of LV dysfunction [42,134]. | I                  | B                  |
| ■ May be considered when the detection of LVH may influence treatment decisions [42,134].                                   | IIb                | B                  |

Continued

| Blood vessels                                                                                                                                                                                        |     |   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|---|
| Ultrasound examination of the carotid arteries:                                                                                                                                                      | I   | B |
| ■ Is recommended in patients with stroke or TIA [134]                                                                                                                                                |     |   |
| ■ May be considered for the detection of asymptomatic atherosclerotic plaques or carotid stenosis in patients with documented vascular disease elsewhere [42].                                       | IIb | B |
| Measurement of PWV may be considered for measuring arterial stiffness [109,189].                                                                                                                     | IIb | B |
| Measurement of ABI may be considered for the detection of advanced LEAD [153,190].                                                                                                                   | IIb | B |
| Kidney                                                                                                                                                                                               |     |   |
| Measurement of serum creatinine and eGFR is recommended in all hypertensive patients [180].                                                                                                          | I   | B |
| Measurement of urine albumin:creatinine ratio is recommended in all hypertensive patients [43,180].                                                                                                  | I   | B |
| Renal ultrasound and Doppler examination should be considered in patients with impaired renal function, albuminuria, or for suspected secondary hypertension.                                        | IIa | C |
| Fundoscopy                                                                                                                                                                                           |     |   |
| Is recommended in patients with grades 2 or 3 hypertension and all hypertensive patients with diabetes.                                                                                              | I   | C |
| May be considered in other hypertensive patients.                                                                                                                                                    | IIb | C |
| Brain                                                                                                                                                                                                |     |   |
| In hypertensive patients with neurological symptoms and/or cognitive decline, brain MRI or CT should be considered for detecting brain infarctions, microbleeds, and white matter lesions [168,169]. | IIa | B |

Abbreviations: ABI, ankle-brachial index; CKD, chronic kidney disease; CT, computed tomography; eGFR, estimated glomerular filtration rate; HMOD, hypertension-mediated organ damage; LEAD, lower extremity artery disease; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; PWV, pulse wave velocity.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

## GENETICS AND HYPERTENSION

A positive family history is a frequent feature in hypertensive patients, with the heritability estimated to vary between 35 and 50% in most studies [191,192]. However, hypertension is a highly heterogeneous disorder with a multifactorial aetiology. Several genome-wide association studies and their meta-analyses have identified 120 loci that are associated with BP regulation, but together these only explain about 3.5% of the trait variance [193]. Several rare, monogenic forms of hypertension have been described such as glucocorticoid-remediable aldosteronism, Liddle's syndrome, and others, where a single gene mutation fully explains the pathogenesis of hypertension and dictates the best treatment modality [194–196]. There are also inherited forms of pheochromocytoma and paraganglioma, which are also rare causes of hypertension [197–200]. Outside of specialist clinics evaluating patients for these rare causes of secondary hypertension, there is no role for genetic testing in hypertension in routine clinical care.

| Genetic testing and hypertension                                                                                                                                                    |                    |                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Recommendations                                                                                                                                                                     | Class <sup>a</sup> | Level <sup>b</sup> |
| Genetic testing should be considered in specialist centres for patients suspected to have rare monogenic causes of secondary hypertension or for those with pheochromocytoma [198]. | IIa                | B                  |
| Routine genetic testing for hypertensive patients is not recommended.                                                                                                               | III                | C                  |

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

## TREATMENT OF HYPERTENSION

### BENEFICIAL EFFECTS OF BLOOD PRESSURE-LOWERING THERAPY IN HYPERTENSION

There are two well established strategies to lower BP: lifestyle interventions and drug treatment. Device-based therapy is also emerging, but is not yet proven as an effective treatment option. Lifestyle interventions can undoubtedly lower BP and in some cases cardiovascular risk (see section 'Lifestyle changes'), but most patients with hypertension will also require drug treatment. The drug treatment of hypertension is founded on very solid evidence, underpinned by the largest number of outcome-based RCTs in clinical medicine. Meta-analyses of RCTs including several hundred thousand patients have shown that a 10 mmHg reduction in SBP or a 5 mmHg reduction in DBP is associated with significant reductions in all major cardiovascular events by 20%, all-cause mortality by 10–15%, stroke by 35%, coronary events by 20%, and heart failure by 40% [2,8]. These relative risk reductions are consistent, irrespective of baseline BP within the hypertensive range, the level of cardiovascular risk, comorbidities (e.g. diabetes and CKD), age, sex, and ethnicity [2,201].

Relative outcome reductions calculated by two recent meta-analyses are similar to those provided by the original meta-analysis of the effects of BP lowering on outcomes in 1994 [202]. Thus, the benefits of antihypertensive treatment have not been attenuated by the widespread concomitant prescription of lipid-lowering and antiplatelet therapies in contemporary medicine.

Another important objective of antihypertensive therapy is to reduce the development of CKD; however, the slow rate

of decline in renal function in most hypertensive patients makes the demonstration of potential benefits of BP lowering difficult. Consequently, the protective effect of BP reduction on kidney function can be less obvious and has been restricted to patients with diabetes or CKD, in whom there is a faster rate of disease progression [203]. Some, but not all, RCTs have also shown a protective effect of BP lowering on the progression of CKD towards end-stage renal disease in both diabetic and nondiabetic nephropathy [2].

The recommendations that follow are based on outcome evidence from RCTs; however, it must be acknowledged that RCTs based on clinical outcomes have limitations, the most important of which are that the data are largely limited to older and high-risk patients, preferentially recruited to increase statistical power, and over a relatively short duration of follow-up, rarely beyond 5 years. This means that recommendations for life-long treatment for younger and lower risk patients are necessarily based on considerable extrapolation. Big data, now being collected by national health system registries, health insurance companies, and prolonged observational follow-up of RCTs, are becoming an important source of long-term information on the effects of chronic treatment [204], which adds to that provided by observational studies over several decades [205–207]. Such evidence suggests that the benefit of continued treatment is maintained over decades [206].

## WHEN TO INITIATE ANTIHYPERTENSIVE TREATMENT

### RECOMMENDATIONS IN PREVIOUS GUIDELINES

All guidelines agree that patients with grade 2 or 3 hypertension should receive antihypertensive drug treatment alongside lifestyle interventions [208]. Guidelines are also consistent in recommending that patients with grade 1 hypertension and high cardiovascular risk or HMOD should be treated with BP-lowering drugs. There has been less consistency about whether BP-lowering drugs should be offered to patients with grade 1 hypertension and low-moderate cardiovascular risk or grade 1 hypertension in older patients (>60 years), or the need for BP-lowering drug treatment in patients with high-normal BP levels [17,209,210]. This uncertainty relates to the fact that low-risk patients with high-normal BP or grade 1 hypertension have rarely been included in RCTs, and that in older patients, RCTs have invariably recruited patients with at least grade 2 hypertension. New analyses and RCT data have become available in these important areas and are discussed below.

### DRUG TREATMENT FOR PATIENTS WITH GRADE 1 HYPERTENSION AT LOW-MODERATE CARDIOVASCULAR RISK

Recent meta-analyses show significant treatment-induced reductions in cardiovascular events and mortality in patients with grade 1 hypertension [8,201,211]. However, the first of these analyses included a substantial number of patients who had grade 1 hypertension despite existing treatment, and were therefore likely to have had initial BPs above the grade 1 range. Furthermore, many of the patients had diabetes and were therefore at high cardiovascular risk [211]. The second meta-analysis, limited

to RCTs in patients with grade 1 hypertension and low-moderate-risk (five RCTs, 8974 patients), demonstrated a significant reduction in all major cardiovascular events by BP-lowering drug treatment [combined stroke and coronary artery disease (CAD) reduced by 34%, and all-cause mortality by 19% for an SBP reduction of 7 mmHg] [8]. A third analysis demonstrated a benefit of BP lowering in reducing death and CVD in patients with a baseline BP 140/90 mmHg or higher, but not when baseline BP was lower [201]. These findings have been supported by the results of a subgroup analysis of the Heart Outcomes Prevention Evaluation (HOPE)-3 trial, showing a significant 27% reduction in major cardiovascular outcomes in patients at intermediate cardiovascular risk and baseline SBP values in the grade 1 hypertensive range [i.e. >143.5 mmHg (mean 154 mmHg)] when SBP was lowered by drug treatment by a mean of 6 mmHg [212].

Based on these new data, this Task Force now recommends that lifestyle advice should be accompanied by BP-lowering drug treatment in patients with grade 1 hypertension at low-moderate cardiovascular risk.

### INITIATION OF BLOOD PRESSURE-LOWERING DRUG TREATMENT IN OLDER PEOPLE WITH GRADE 1 HYPERTENSION

Discussion about the treatment of 'the elderly' or 'older' people has been complicated by the various definitions of older age used in RCTs. For example, older was defined as more than 60 years in the earliest trials, then as 65, 70 and finally 75 [51] or 80 years [213] in later trials. Chronological age is often a poor surrogate for biological age, with consideration of frailty and independence influencing the likely tolerability of BP-lowering medications. For the purposes of this guideline, the 'old' are defined as at least 65 years and the 'very old' as at least 80 years. The previous Guidelines [17] noted that all available evidence on cardiovascular event reduction by BP lowering in older patients was obtained in patients whose baseline SBP was at least 160 mmHg, and there is strong evidence that these patients should be offered BP-lowering drug treatment [210,214].

Undoubtedly, there are RCTs showing outcome benefits with BP-lowering treatment in older patients whose baseline BP was in a lower SBP range, but these patients were often on background antihypertensive treatment, thus they cannot be defined as having true grade 1 hypertension. This is also the case for the data recently published from the SPRINT trial, which included a cohort of patients older than 75 years, in whom more intense BP lowering reduced the risk of major cardiovascular events and mortality [51,215]. However, in most RCTs showing a protective effect of BP-lowering treatment in patients with an untreated baseline BP in the grade 1 hypertension range, older patients were well represented. This was further supported by the recent HOPE-3 trial, which showed beneficial effects of BP lowering on cardiovascular outcomes in patients, many with grade 1 hypertension (SBP >143 mmHg and mean BP 154 mmHg), whose mean age was 66 years, and in whom only 22% had prior treatment of hypertension [212].

The evidence supports the recommendation that older patients (>65 years, including patients over 80 years) should be offered BP-lowering treatment if their SBP is at least 160 mmHg. There is also justification to now recommend BP-lowering treatment for old patients (aged >65 but



not >80 years) at a lower BP (i.e. grade 1 hypertension; SBP 140–159 mmHg) [201]. BP-lowering drugs should not be withdrawn on the basis of age alone. It is well established that BP-lowering treatment withdrawal leads to a marked increase in cardiovascular risk. This was exemplified in older patients by a recent subgroup analysis of the Hypertension in the Very Elderly Trial (HYVET) [213], reporting that in patients aged at least 80 years, cardiovascular risk reduction was greatest in those who continued treatment rather than in those whose treatment was discontinued [216]. As stated above, all of the above recommendations relate to relatively fit and independent older patients, because physically and mentally frail and institutionalized patients have been excluded in most RCTs of patients with hypertension [214]. Further details of the treatment of hypertension in older patients and very old patients is provided in section ‘Hypertension in older patients (Age 65 years)’.

### INITIATION OF BLOOD PRESSURE-LOWERING DRUG TREATMENT IN PATIENTS WITH HIGH-NORMAL BLOOD PRESSURE

The previous (2013) Guidelines [17] recommended not to initiate antihypertensive treatment in people with high-normal BP and low-moderate cardiovascular risk. This recommendation is further supported by new evidence:

1. In all RCTs (including SPRINT) [51] and meta-analyses [2] that have reported reduced major outcomes by lowering ‘baseline’ BP in the high-normal range, the ‘baseline’ BP was commonly measured on a background of antihypertensive treatment. Therefore, these studies do not provide evidence to support treatment initiation in patients without hypertension [8].
2. The HOPE-3 trial [212], in which only 22% of the patients at intermediate cardiovascular risk had background antihypertensive treatment, showed that BP-lowering treatment did not reduce the risk of major cardiovascular events in patients with baseline SBP values in the high-normal range.
3. A meta-analysis of 13 RCTs or RCT subgroups (involving 21 128 individuals) in patients at low-moderate cardiovascular risk and untreated baseline BP in the high-normal and normal range, showed no effect of BP-lowering treatment on any cardiovascular outcomes [217].
4. Another recent analysis, including patients with high-normal BP, concluded that primary preventive BP lowering was associated with reduced risk for death and incident CVD if baseline SBP was 140 mmHg or higher, but at lower BP levels [i.e. high-normal BP (<140/90 mmHg)], treatment was not associated with any benefit in primary prevention [201].
5. The situation may be different in very high-risk patients with a high-normal BP and established CVD. In a meta-analysis of 10 RCTs or RCT subgroups that also included individuals at high or very high cardiovascular risk, mostly with previous CVD and untreated high-normal and normal BP ( $n$  26 863), BP-lowering drug treatment, achieving an SBP reduction of 4 mmHg, reduced the risk of stroke but not any other cardiovascular events [217]. In another analysis of trials including people with previous CAD and a mean baseline SBP of 138 mmHg, treatment was associated with reduced risk for major

cardiovascular events (relative risk 0.90; 95% confidence interval 0.84–0.97), but was not associated with an increased survival (relative risk 0.98; 95% confidence interval 0.89–1.07) [201]. Thus, the benefit for treating people with high-normal BP appears marginal and, if present, appears to be restricted to those at very high cardiovascular risk and established CVD, especially CAD.

We recommend that patients with high-normal BP and low-moderate cardiovascular risk should be offered lifestyle advice, because this reduces their risk of progressing to established hypertension and may further reduce their cardiovascular risk. These patients should not be offered BP-lowering drug treatment. Nevertheless, based on the data from the HOPE-3 trial, drug treatment may be considered in these patients if their BP is close to the hypertension diagnostic threshold of 140/90 mmHg, after a prolonged attempt to control BP with lifestyle changes.

BP-lowering drugs may be considered for patients with high-normal BP and established CVD, especially CAD. In these patients, monotherapy may be sufficient.

### SHOULD BLOOD PRESSURE-LOWERING DRUG TREATMENT BE INITIATED ON THE BASIS OF BLOOD PRESSURE VALUES OR THE LEVEL OF TOTAL CARDIOVASCULAR RISK?

Two recent meta-analyses of RCTs [8,218] have shown that when BP-lowering data are stratified according to cardiovascular risk, the relative risk reductions do not differ across the various risk strata; not surprisingly, the absolute risk reduction is greater with increasing baseline cardiovascular risk. These data have been taken as support for the hypothesis that BP-lowering treatment should be based on cardiovascular risk and target those at greatest cardiovascular risk, irrespective of their BP [218]. However, it has recently been made that whereas patients at high or very high cardiovascular risk exhibit the greatest absolute reduction in cardiovascular outcomes with BP-lowering treatment, they also have the highest residual risk, which means failure of treatment to exert full protection [8]. It is the opinion of this Task Force that these data support earlier treatment of patients with SBP or DBP values more than 140/90 mmHg when their cardiovascular risk is still low-moderate, to prevent the accumulation of HMOD and a high incidence of late treatment failure (residual risk), which would otherwise occur if treatment was delayed by a purely cardiovascular risk-based approach. The most effective strategy to reduce risk is to prevent the development of high cardiovascular-risk situations with earlier intervention. The assessment of cardiovascular risk is at the core of the treatment strategy recommended by these Guidelines because of the frequent coexistence of multiple cardiovascular risk factors in hypertensive patients, and to inform the use of concomitant medications (e.g. statins, antiplatelet therapies, etc., see section ‘Managing concomitant cardiovascular disease risk’) to reduce cardiovascular risk. We conclude that, in general, the decision to use BP-lowering treatment should not be based solely on the level of cardiovascular risk because even in patients at the highest risk (with established CVD), when baseline BP is below 140/90 mmHg, the benefits of BP-lowering treatment are at best marginal and most evident in patients with CAD at the upper end of the high-normal BP range [201].



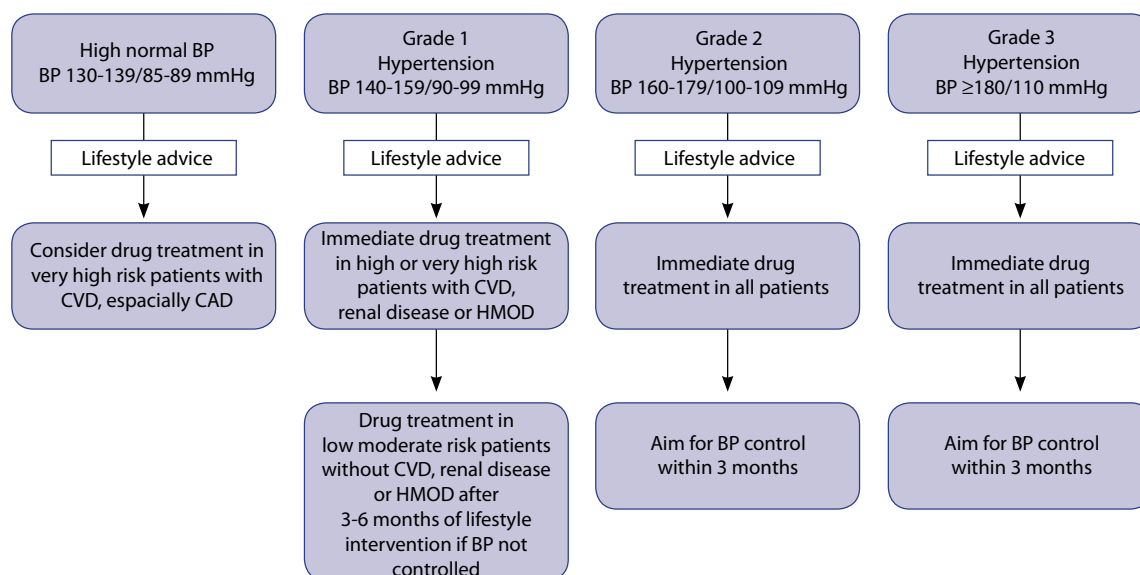


**Figure 65.3** Initiation of blood pressure-lowering treatment (lifestyle changes and medication) at different initial office blood pressure levels. *Abbreviations:* BP, blood pressure; CAD, coronary artery disease; CVD, cardiovascular disease; HMOD, hypertension-mediated organ damage.

### INITIATION OF BLOOD PRESSURE-LOWERING DRUG TREATMENT

In patients with grade 2 or 3 hypertension, it is recommended that BP-lowering drug treatment should be initiated alongside lifestyle interventions. In patients with grade 1 hypertension at high risk or with HMOD, drug treatment should

also be initiated simultaneously with lifestyle interventions. In lower-risk patients with grade 1 hypertension, BP-lowering drug treatment should be initiated after 3–6 months if BP is not controlled by lifestyle interventions alone (Figure 65.3). Recommended BP thresholds for the initiation of antihypertensive drug treatment are shown in Table 65.19.

| Initiation of hypertension treatment according to office BP                                                                                                                                                                               |                    |                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Recommendations                                                                                                                                                                                                                           | Class <sup>a</sup> | Level <sup>b</sup> |
| Prompt initiation of BP-lowering drug treatment is recommended in patients with grade 2 or 3 hypertension at any level of CV risk, simultaneous with the initiation of lifestyle changes [2,8].                                           | I                  | A                  |
| In patients with grade 1 hypertension:                                                                                                                                                                                                    | II                 | B                  |
| ■ Lifestyle interventions are recommended to determine if this will normalize BP [219].                                                                                                                                                   | I                  | A                  |
| ■ In patients with grade 1 hypertension at low–moderate risk and without evidence of HMOD, BP-lowering drug treatment is recommended if the patient remains hypertensive after a period of lifestyle intervention <sup>c</sup> [211,212]. | I                  | A                  |
| ■ In patients with grade 1 hypertension and at high risk or with evidence of HMOD, prompt initiation of drug treatment is recommended simultaneously with lifestyle interventions [211,212].                                              | I                  | A                  |
| In fit older patients with hypertension (even if aged >80 years), BP-lowering drug treatment and lifestyle intervention are recommended when SBP is ≥160 mmHg [210,220,221].                                                              | I                  | A                  |
| BP-lowering drug treatment and lifestyle intervention are recommended for fit older patients (>65 years but not >80 years) when SBP is in the grade 1 range (140–159 mmHg), provided that treatment is well tolerated [212].              | I                  | A                  |
| Antihypertensive treatment may also be considered in frail older patients if tolerated [215].                                                                                                                                             | IIb                | B                  |
| Withdrawal of BP-lowering drug treatment on the basis of age, even when patients attain an age of ≥80 years, is not recommended, provided that treatment is well tolerated [213].                                                         | III                | A                  |
| In patients with high-normal BP (130–139/85–89 mmHg):                                                                                                                                                                                     | I                  | A                  |
| ■ Lifestyle changes are recommended [17,35].                                                                                                                                                                                              | IIb                | A                  |
| ■ Drug treatment may be considered when their cardiovascular risk is very high due to established CVD, especially CAD [217].                                                                                                              |                    |                    |

*Abbreviations:* BP, blood pressure; CAD, coronary artery disease; CVD, cardiovascular disease; HMOD, hypertension-mediated organ damage.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

<sup>c</sup> In patients with grade 1 hypertension and at low–moderate-risk, drug treatment may be preceded by a prolonged period of lifestyle intervention to determine if this approach will normalize BP. The duration of the lifestyle intervention alone will depend on the level of BP within the grade 1 range, that is the likelihood of achieving BP control with lifestyle intervention alone, and the opportunities for significant lifestyle change in individual patients.

**Table 65.19** Summary of office blood pressure thresholds for treatment

| Age group                                    | Office SBP treatment threshold (mmHg) |            |       |                   |                   | Office DBP treatment threshold (mmHg) |
|----------------------------------------------|---------------------------------------|------------|-------|-------------------|-------------------|---------------------------------------|
|                                              | Hypertension                          | + Diabetes | + CKD | + CAD             | + Stroke/TIA      |                                       |
| 18–65 years                                  | ≥140                                  | ≥140       | ≥140  | ≥140 <sup>a</sup> | ≥140 <sup>a</sup> | ≥90                                   |
| 65–79 years                                  | ≥140                                  | ≥140       | ≥140  | ≥140 <sup>a</sup> | ≥140 <sup>a</sup> | ≥90                                   |
| >80 years                                    | ≥160                                  | ≥160       | ≥160  | ≥160              | ≥160              | ≥90                                   |
| <b>Office DBP treatment threshold (mmHg)</b> | ≥90                                   | ≥90        | ≥90   | ≥90               | ≥90               |                                       |

Abbreviations: BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; TIA, transient ischaemic attack.

<sup>a</sup> Treatment may be considered in these very high-risk patients with high-normal SBP (i.e. SBP 130–140 mmHg).

## BLOOD PRESSURE TREATMENT TARGETS

### NEW EVIDENCE ON SYSTOLIC BLOOD PRESSURE AND DIASTOLIC BLOOD PRESSURE TREATMENT TARGETS

The 2013 ESH/ESC hypertension Guidelines [17] recommended an office BP treatment target of <140/90 mmHg, regardless of the number of comorbidities and level of cardiovascular risk. The Guidelines specifically stated that evidence from RCTs, meta-analyses, and post hoc analysis of large-scale RCTs all showed no obvious incremental benefit of lowering BP to less than 130/80 mmHg. Since then, new information has emerged from post hoc analyses of large outcome trials in patients at high cardiovascular risk [222–224], registries in patients with coronary disease, and, more importantly, new RCTs and meta-analyses of all available RCT evidence. In the post hoc RCT analyses and registry data, compared with a target SBP of between 130 and 139 mmHg, lowering SBP to less than 130 mmHg was, in general, associated with no further benefit on major cardiovascular events, except perhaps for further reductions in the risk of stroke. A consistent finding was that reducing SBP to less than 120 mmHg increased the incidence of cardiovascular events and death.

A recent RCT relevant to the issue of target BP is SPRINT, which compared two different SBP targets (<140 or <120 mmHg) in more than 9000 patients at high cardiovascular risk, but excluded patients with diabetes or previous stroke. More intensive BP-lowering treatment (achieved SBP 121 vs. 136 mmHg) was associated with a 25% reduction in major cardiovascular events and a 27% reduction in all-cause death (but no significant reduction in stroke or myocardial infarction) [51]. This outcome unquestionably provides strong support for the beneficial effects of more vs. less intensive BP-lowering treatment strategies in higher risk patients. However, this RCT does not clarify the optimal BP target because the method used for office BP measurement in SPRINT (unattended automatic measurement) had not been used in any previous RCTs that provide the evidence base for the treatment of hypertension [225]. This is because unattended automated office BP measurement results in lower BP values, relative to conventional office BP measurement, due to the absence of the white-coat effect [52,54]. Thus, it has been suggested that the BP values reported in SPRINT may correspond to conventional office SBPs in the 130–140 and 140–150 mmHg ranges in the more vs. less intensive BP-lowering groups, respectively.

Some new information on SBP and DBP targets for drug treatment has been provided by two recent, large

meta-analyses of RCTs of BP lowering. In the first of these meta-analyses, achieved SBP was stratified according to three SBP target ranges (149–140, 139–130 and <130 mmHg) [226]. Lowering SBP to less than 140 mmHg reduced the relative risk of all major cardiovascular outcomes (including mortality); similar benefits were seen when SBP was lowered to less than 130 mmHg (average 126 mmHg). Importantly, the latter was also true when the achieved SBP in the comparator group was 130–139 mmHg. Stratification of RCTs for achieved DBP, to either 89–80 or less than 80 mmHg, also showed a reduction in all types of cardiovascular outcomes compared with higher DBP values [226].

The second meta-analysis, which also included the SPRINT trial [2], noted that every 10 mmHg reduction in SBP reduced the rate of major cardiovascular events and death for baseline SBP values more than 160 mmHg to baseline values between 130 and 139 mmHg, implying benefit at achieved SBP values of less than 130 mmHg. Furthermore, a benefit of a 10 mmHg reduction in SBP was also reported for patients with a baseline SBP of less than 130 mmHg, thereby achieving values less than 120 mmHg. However, there were far fewer patients in these subgroups, and this last set of data will have been heavily influenced by the unusually low BP values in the SPRINT trial, due to the method of BP measurement (see above). Importantly, this analysis showed consistent benefit from intensive BP lowering in patients at all levels of risk, including those with and without existing CVD, stroke, diabetes and CKD.

Finally, in the first meta-analysis [226], the incremental benefit of BP lowering on events progressively decreased as the target BP was lowered. Furthermore, an additional meta-analysis by the same group found that permanent treatment discontinuation because of treatment-related adverse effects was significantly higher in those targeted to lower BP values [227]. Therefore, advocating more intensive BP-lowering targets for all has to be viewed in the context of an increased risk of treatment discontinuation due to adverse events, which might offset, in part or completely, the limited incremental reduction in cardiovascular risk.

Whilst considering BP targets, it is important to acknowledge that less than 50% of patients treated for hypertension currently achieve a target office SBP of less than 140 mmHg [11,12]. This is a major missed opportunity for CVD prevention in millions of people across the world.

This Task Force recommends that when BP-lowering drugs are used, the first objective should be to lower BP to <140/90 mmHg in all patients. Provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients, although in

some groups the evidence is less compelling. In older patients (>65 years), SBP should be targeted to between 130 and 140 mmHg, and DBP to less than 80 mmHg. Treated SBP should not be targeted to less than 120 mmHg.

Importantly, we specify a target range because the lower safety boundary assumes greater importance when BP is targeted to lower levels. Furthermore, in general, when SBP is lowered to less than 120 mmHg in patients included in RCTs (i.e. older and higher-risk patients, often with comorbidities and CVD), the risk of harm appears to increase and outweigh the benefits [222].

## BLOOD PRESSURE TARGETS IN SPECIFIC SUBGROUPS OF HYPERTENSIVE PATIENTS

### DIABETES MELLITUS

RCTs in type 1 diabetes mellitus demonstrate that BP-lowering treatment has a renoprotective effect [228], but because these patients tend to be younger, previous RCTs have had inadequate power to study cardiovascular outcomes and to establish optimal BP targets.

In contrast, there have been many BP-lowering treatment RCTs, either exclusively dedicated to patients with type 2 diabetes or hypertension trials that have included a large cohort of patients with type 2 diabetes [2]. Most of these RCTs have shown that BP lowering to less than 140/85 mmHg is beneficial in patients with type 2 diabetes and hypertension. However, the results have been less clear about whether a lower BP target is associated with further benefits. The evidence can be summarized as follows:

1. A large RCT in patients with type 2 diabetes has shown that an achieved SBP of less than 135 mmHg, compared with 140 mmHg, was associated with a significant reduction in cardiovascular and all-cause mortality [229].
2. Evidence from another large RCT in patients with type 2 diabetes showed that, compared with patients with an on-treatment SBP of 135 mmHg, reducing SBP to 121 mmHg did not reduce cardiovascular morbidity and mortality or all-cause death, but substantially reduced the risk of stroke [230].
3. Although one recent meta-analysis concluded that most of the benefit associated with BP lowering was obtained at higher BP targets (i.e. <150 mmHg but not <140 mmHg) [231], other large meta-analyses have confirmed that in type 2 diabetes, lowering SBP to <140 mmHg is associated with reductions in all major cardiovascular events [1,232–234].
4. Two of the meta-analyses concluded that the overall benefit of lowering BP in patients with type 2 diabetes (unlike patients without type 2 diabetes) largely disappears when SBP is lowered to less than 130/80 mmHg [1,235], except for the continuing incremental benefit on stroke.
5. Similar evidence for stroke benefit from lower achieved SBP has also been reported from posthoc analysis of diabetic patients in the ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) study. In addition, reanalysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) [230] trial in type 2 diabetes, after removing the interaction from the intensive glucose-lowering arm and thereby limiting the analysis to BP-lowering effects, showed an overall

reduction in cardiovascular events with intensive SBP lowering to less than 130 mmHg [236].

6. Further recent analysis of the ACCORD trial has shown that reducing SBP to less than 120 mmHg was associated with increased risk of major cardiovascular events [236].
7. With regard to DBP, earlier evidence suggested a benefit on major cardiovascular events when DBP was lowered to less than 85 mmHg [237,238]. More recently, in the Action in Diabetes and Vascular Disease: Preterax and Diamicon – MR Controlled Evaluation (ADVANCE) trial [229], the benefits on cardiovascular outcomes were observed at diastolic pressures of 75 mmHg. This is consistent with evidence from the meta-analyses cited above, that it is safe and effective to lower DBP to less than 80 mmHg in patients with type 2 diabetes.

In summary, in patients with diabetes receiving BP-lowering drugs, it is recommended that office BP should be targeted to an SBP of 130 mmHg [229], and lower if tolerated. In older patients (aged  $\geq 65$  years) the SBP target range should be 130–140 mmHg [213] if tolerated. SBP should not be lowered to less than 120 mmHg and DBP should be lowered to less than 80 mmHg. Attention should also be given to the consistency of BP control, because visit-to-visit BP variability is associated with increased cardiovascular and renal disease risk. Furthermore, cardiovascular protection has been found to be greater when BP control is accompanied by fewer visit-to-visit BP variations [239–241].

### OLDER PATIENTS

The definition of ‘older’ is complex. As populations age, there is increasingly wide variation between a patient’s chronological age and their functional status, ranging from fit, active, and independent, through to frail and dependent. The anticipated benefits vs. potential harm of BP treatment in older patients will be influenced by the patient’s ability to tolerate treatment and their health and functional status. For the purposes of these Guidelines, ‘older’ patients are defined as those aged at least 65 years.

In the 2013 ESH/ESC hypertension Guidelines, the target SBP for older hypertensive patients was set at 140–150 mmHg because this was the range of systolic values achieved by major outcome trials demonstrating a beneficial effect of antihypertensive treatment in these patients. A similar SBP target was suggested by the HYVET trial, in which treating to an SBP target of less than 150 mmHg (achieving a mean SBP of 144 mmHg) in the very old (>80 years) demonstrated significant reductions in mortality, fatal stroke, and heart failure, with the caveat that the ‘very old’ patients in this study were active and independent [213]. More recent evidence supports a lower SBP target for older patients ( $\geq 65$  years):

1. The SPRINT trial included a high proportion of patients over the age of 75 years ( $n = 2636$ ) and demonstrated that more intensive BP-lowering treatment (mean achieved BP = 124/62 mmHg) significantly reduced the risk of major cardiovascular events, heart failure, and all-cause death (all by >30%) compared with standard treatment (mean achieved BP = 135/67 mmHg) [215]. It has been noted above that the BP measurement technique used in SPRINT generated lower values than those provided by the conventional office

BP measurement [225,242]. Consequently, the SBP of 124 mmHg achieved in the intensively treated older patients in the SPRINT trial most probably reflects a conventional office SBP range of 130–139 mmHg.

- Although HYVET and most other RCTs in older patients have recruited relatively fit and independent patients, the SPRINT study also suggested that there are benefits of more intensive treatment being extended to older patients who are at the frailer end of the spectrum of patients meeting the recruitment criteria, with reduced gait speed [215].

Based on the new data, the targets suggested by the previous Guidelines now appear too conservative for many old and very old patients, especially those who are active and independent. Consequently, we recommend that in older patients treated for hypertension, BP should be lowered to less than 140/80 mmHg, but not below an SBP of 130 mmHg. Importantly, the impact of BP lowering on the well being of the patient should be closely monitored, because the increased risk of adverse events (e.g. injurious falls) with lower BP values could be more pronounced in older patients in the real-life setting than in the closely monitored conditions of RCTs. Further details on the approach to treatment of the frail older patient are discussed in section 'Hypertension in older patients (Age 65 years)'.

#### OFFICE VS. HOME AND AMBULATORY BLOOD PRESSURE TARGETS

No outcome-based RCT has used ABPM or HBPM to guide the treatment of hypertension. Thus, ABPM and HBPM BP targets are based on extrapolation from observational data rather than on outcome trials. Although we do not provide formal ABPM or HBPM BP targets for treated patients, it should be noted that:

- In population studies, the difference between office and out-of-office BP levels decreases as office BP decreases, to a point of around 115–120/70 mmHg, at which office and 24 h ABPM mean BP values are usually similar [54].
- This convergence has also been confirmed in treated patients [243] in whom the difference between office BP and ambulatory BP values diminishes and becomes negligible at an SBP of approximately 120 mmHg.
- In treated patients, a target office SBP of 130 mmHg might therefore correspond to a slightly lower mean 24 h SBP, that is approximately 125 mmHg.
- Although there are no available data, the home SBP target, to be equivalent to an office SBP target of 130 mmHg, might also be lower than 130 mmHg.

| Office BP treatment targets in hypertensive patients                                                                                                                                                                                                   |                    |                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Recommendations                                                                                                                                                                                                                                        | Class <sup>a</sup> | Level <sup>b</sup> |
| It is recommended that the first objective of treatment should be to lower BP to <140/90 mmHg in all patients and, provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients [2,8]. | I                  | A                  |

Continued

|                                                                                                                                                                                                                                                                                                                                                                       |     |   |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|---|
| In patients <65 years receiving BP-lowering drugs, it is recommended that SBP should be lowered to a BP range of 120–129 mmHg in most patients [2,215,229]. <sup>c</sup>                                                                                                                                                                                              | I   | A |
| In older patients (aged ≥65 years) receiving BP-lowering drugs:<br>■ It is recommended that SBP should be targeted to a BP range of 130–139 mmHg [2,235,244].<br>■ Close monitoring of adverse effects is recommended.<br>■ These BP targets are recommended for patients at any level of cardiovascular risk and in patients with and without established CVD [2,8]. | I   | A |
|                                                                                                                                                                                                                                                                                                                                                                       | I   | C |
|                                                                                                                                                                                                                                                                                                                                                                       | I   | A |
| A DBP target of <80 mmHg should be considered for all hypertensive patients, independent of the level of risk and comorbidities [226,235].                                                                                                                                                                                                                            | IIa | B |

Abbreviations: BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

<sup>c</sup> Less evidence is available for this target in low–moderate-risk patients.

## TREATMENT OF HYPERTENSION

### LIFESTYLE CHANGES

Healthy lifestyle choices can prevent or delay the onset of hypertension and can reduce cardiovascular risk [17,35]. Effective lifestyle changes may be sufficient to delay or prevent the need for drug therapy in patients with grade 1 hypertension. They can also augment the effects of BP-lowering therapy, but they should never delay the initiation of drug therapy in patients with HMOD or at a high level of cardiovascular risk. A major drawback of lifestyle modification is the poor persistence over time [245,246]. The recommended lifestyle measures that have been shown to reduce BP are salt restriction, moderation of alcohol consumption, high consumption of vegetables and fruits, weight reduction and maintaining an ideal body weight, and regular physical activity [17]. In addition, tobacco smoking has an acute prolonged pressor effect that may raise daytime ambulatory BP, but smoking cessation and other lifestyle measures are also important beyond BP (i.e. for CVD and cancer prevention) [35].

### DIETARY SODIUM RESTRICTION

There is evidence of a causal relationship between sodium intake and BP, and excessive sodium consumption (>5 g sodium per day, e.g. one small teaspoon of salt per day) has been shown to have a pressor effect and be associated with an increased prevalence of hypertension and the rise in SBP with age [247]. Conversely, sodium restriction has been shown to have a BP-lowering effect in many trials. A recent meta-analysis of these trials showed that a reduction of 1.75 g sodium per day (4.4 g salt per day) was associated with a mean 4.2/2.1 mmHg reduction in SBP/DBP, with a more pronounced effect (−5.4/−2.8 mmHg) in people with hypertension [248]. The beneficial effect of a reduced sodium intake on BP tends to diminish with time,



in part due to poor dietary persistence. The BP-lowering effect of sodium restriction is greater in black people, in older patients, and in patients with diabetes, metabolic syndrome, or CKD [249]. In people with treated hypertension, effective sodium restriction may reduce the number or dose of BP-lowering drugs that are necessary to control BP [250,251].

The effect of reduced dietary sodium on cardiovascular events remains unclear [252–255]. Prospective cohort studies have reported an overall increased risk of mortality and cardiovascular events on high sodium intake. However, they also reported that reducing sodium intake below a certain level (about 3 g of sodium per day) further reduced BP, but paradoxically was associated with an increased risk of all-cause and cardiovascular mortalities in both the general population and in hypertensive people, suggesting a J-curve phenomenon [256]. The mechanism of this apparent increased risk at low sodium intake is not well understood and might be confounded by reverse causality. There is no evidence from epidemiological studies that very low sodium intake may cause harm [257]. Although a few trials and meta-analyses suggest that reducing salt intake from high to moderate is accompanied by a lower risk of cardiovascular events [254,255,258], to date, no prospective RCT has provided definitive evidence about the optimal sodium intake to minimize cardiovascular events and mortality. Increased potassium intake is associated with BP reduction and may have a protective effect, thereby modifying the association between sodium intake, BP and CVD [259].

Globally, usual sodium intake is between 3.5 and 5.5 g/day (which corresponds to 9–12 g of salt per day), with marked differences between countries and even between regions within countries. We recommend sodium intake to be limited to approximately 2.0 g/day (equivalent to approximately 5.0 g salt per day) in the general population and to try to achieve this goal in all hypertensive patients. Effective salt reduction is not easy and there is often poor appreciation of which foods contain high salt levels. Advice should be given to avoid added salt and high-salt foods. A reduction in population salt intake remains a public health priority but requires a combined effort between the food industry, governments, and the public in general, as 80% of salt consumption involves hidden salt in processed foods.

### MODERATION OF ALCOHOL CONSUMPTION

There is a long-established positive linear association between alcohol consumption, BP, the prevalence of hypertension and CVD risk. Binge drinking can have a strong pressor effect [17]. The Prevention and Treatment of Hypertension Study (PATHS) investigated the effects of alcohol reduction on BP; the intervention group had a modest 1.2/0.7 mmHg lower BP than the control group at the end of the 6-month period [260]. A Mendelian randomization meta-analysis of 56 epidemiological studies suggested that reduction of alcohol consumption, even for light-moderate drinkers, might be beneficial for cardiovascular health [261]. Hypertensive men who drink alcohol should be advised to limit their consumption to 14 and women to 8 units per week (1 unit is equal to 125 mL of wine or 250 mL of beer). Alcohol-free days during the week and avoidance of binge drinking [35] are also advised.

### OTHER DIETARY CHANGES

Hypertensive patients should be advised to eat a healthy balanced diet containing vegetables, legumes, fresh fruits, low-fat dairy products, whole grains, fish, and unsaturated fatty acids (especially olive oil), and to have a low consumption of red meat and saturated fatty acids [262–264]. The Mediterranean diet includes many of these nutrients and foods, with a moderate consumption of alcohol (mostly wine with meals). A number of studies and meta-analyses [262–265] have shown that the Mediterranean diet is associated with a reduction in cardiovascular events and all-cause mortality. An RCT in high-risk individuals on the Mediterranean diet over 5 years showed a 29% cardiovascular risk reduction compared with a low-fat control diet, and a 39% reduction in stroke [265]. The Mediterranean diet also significantly reduced ambulatory BP, blood glucose, and lipid levels [266]. The diet should be accompanied by other lifestyle changes such as physical exercise and weight loss [35].

With regard to coffee consumption, caffeine has been shown to have an acute pressor effect [267]. Nevertheless, coffee consumption is associated with cardiovascular benefits, as highlighted by a recent systematic review of prospective cohort studies including more than 1 million participants and 36–352 cardiovascular events [267]. Moreover, green or black tea consumption may also have a small but significant BP-lowering effect [268,269].

Regular consumption of sugar-sweetened soft drinks has been associated with overweight, metabolic syndrome, type 2 diabetes, and higher cardiovascular risk. The consumption of these drinks should be discouraged [35].

Thus, adopting a healthy and balanced diet may assist in BP reduction and also reduce cardiovascular risk.

### WEIGHT REDUCTION

Excessive weight gain is associated with hypertension, and reducing weight towards an ideal body weight decreases BP [270]. In a meta-analysis, the mean SBP and DBP reductions associated with an average weight loss of 5.1 kg were 4.4 and 3.6 mmHg, respectively [271]. Both overweight and obesity are associated with an increased risk of cardiovascular death and all-cause mortality. Weight reduction is recommended in overweight and obese hypertensive patients for control of metabolic risk factors, but weight stabilization may be a reasonable goal for many. The Prospective Studies Collaboration [272] concluded that mortality was lowest at a BMI of approximately 22.5–25 kg/m<sup>2</sup>, whereas a more recent meta-analysis concluded that mortality was lowest in subjects with overweight [273,274]. Although the optimal BMI is unclear, maintenance of a healthy body weight (BMI of approximately 20–25 kg/m<sup>2</sup> in people <60 years of age; higher in older patients) and waist circumference (<94 cm for men and <80 cm for women) is recommended for nonhypertensive individuals to prevent hypertension, and for hypertensive patients to reduce BP [35]. Weight loss can also improve the efficacy of antihypertensive medications and the cardiovascular risk profile. Weight loss should employ a multidisciplinary approach that includes dietary advice, regular exercise, and motivational counselling [35,275]. Furthermore, short-term results are often not maintained over the long-term. Weight loss can also be promoted by antiobesity drugs and, to a greater degree, bariatric surgery, which appears to decrease cardiovascular risk in



severely obese patients. Further details are available in a recent document of the ESH and the European Association for the Study of Obesity [276].

## REGULAR PHYSICAL ACTIVITY

Physical activity induces an acute rise in BP, especially SBP, followed by a short-lived decline in BP below baseline. Epidemiological studies suggest that regular aerobic physical activity may be beneficial for both the prevention and treatment of hypertension, and to lower cardiovascular risk and mortality. A meta-analysis of RCTs, which rely on self-reported exercise and are by necessity unblinded, has shown that aerobic endurance training, dynamic resistance training and isometric training reduce resting SBP and DBP by 3.5/2.5, 1.8/3.2 and 10.9/6.2 mmHg, respectively, in general populations [277]. Endurance training, but not other types of training, reduces BP more in hypertensive participants (8.3/5.2 mmHg). Regular physical activity of lower intensity and duration lowers BP less than moderate-intensity or high-intensity training, but is associated with at least a 15% decrease in mortality in cohort studies [278,279]. This evidence suggests that hypertensive patients should be advised to participate in at least 30 min of moderate intensity dynamic aerobic exercise (walking, jogging, cycling or swimming) on 5–7 days/week. Performance of resistance exercises on 2–3 days/week can also be advised. For additional benefit in healthy adults, a gradual increase in aerobic physical activity to 300 min a week of moderate intensity or 150 min a week of vigorous-intensity aerobic physical activity, or an equivalent combination thereof, is recommended [35]. The impact of isometric exercises on BP and cardiovascular risk is less well established [280].

## SMOKING CESSATION

Smoking is a major risk factor for CVD and cancer. Although the rate of smoking is declining in most European countries, especially in men, it is still common in many regions and age groups, and overall the prevalence remains high at 20–35% in Europe [281]. There is also evidence suggesting ill-health effects of passive smoking [282]. Studies using ABPM have shown that both normotensive subjects and untreated hypertensive smokers present higher daily BP values than nonsmokers [283]. No chronic effect of smoking has been reported for office BP [284], which is not lowered by smoking cessation. Smoking is second only to BP in contributing risk to the global burden of disease, and smoking cessation is probably the single most effective lifestyle measure for the prevention of CVD, including stroke, myocardial infarction, and PAD [285,286]. Therefore, the history of tobacco use should be established at each patient visit and hypertensive smokers should be counselled regarding smoking cessation. Brief advice from a physician has a small but significant effect of 1–3% over and above the unassisted 12-month quit rate [287]. This can be improved by the use of pharmacological measures, with varenicline and combination nicotine replacement therapy being superior to bupropion or single nicotine replacement therapy [288]. In comparison with placebo, nicotine replacement therapy or treatment with bupropion doubles the chance of quitting, while varenicline or combination nicotine replacement therapy triples the chance of quitting. Combining behavioural support

with pharmacotherapy increases the chance of success by 70–100% compared with brief advice alone [289].

## Lifestyle interventions for patients with hypertension or high-normal BP

| Recommendations                                                                                                                                                                                                                                                                                                               | Class <sup>a</sup> | Level <sup>b</sup> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Salt restriction to <5 g per day is recommended [248,250,255,258].                                                                                                                                                                                                                                                            | I                  | A                  |
| It is recommended to restrict alcohol consumption to:<br>■ Less than 14 units per week for men.<br>■ Less than 8 units per week for women [35].                                                                                                                                                                               | I                  | A                  |
| It is recommended to avoid binge drinking.                                                                                                                                                                                                                                                                                    | III                | C                  |
| Increased consumption of vegetables, fresh fruits, fish, nuts, and unsaturated fatty acids (olive oil); low consumption of red meat; and consumption of low-fat dairy products are recommended [262,265].                                                                                                                     | I                  | A                  |
| Body-weight control is indicated to avoid obesity (BMI >30 kg/m <sup>2</sup> or waist circumference >102 cm in men and >88 cm in women), as is aiming at healthy BMI (about 20–25 kg/m <sup>2</sup> and waist circumference values <94 cm in men and <80 cm in women) to reduce BP and cardiovascular risk [262,271,273,290]. | I                  | A                  |
| Regular aerobic exercise (e.g. at least 30 min of moderate dynamic exercise on 5–7 days per week) is recommended [262,278,279].                                                                                                                                                                                               | I                  | A                  |
| Smoking cessation, supportive care, and referral to smoking cessation programs are recommended [286,288,291].                                                                                                                                                                                                                 | I                  | B                  |

Abbreviations: BMI, body mass index; BP, blood pressure.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence mostly based on the effect on BP and/or cardiovascular risk profile.

## PHARMACOLOGICAL THERAPY FOR HYPERTENSION

### DRUGS FOR THE TREATMENT OF HYPERTENSION

Most patients will require drug therapy in addition to lifestyle measures to achieve optimal BP control. In the previous Guidelines, five major drug classes were recommended for the treatment of hypertension: ACE inhibitors, ARBs, beta-blockers, CCBs, and diuretics (thiazides and thiazide-like diuretics such as chlorthalidone and indapamide), based on: proven ability to reduce BP; evidence from placebo-controlled studies that they reduce cardiovascular events; and evidence of broad equivalence on overall cardiovascular morbidity and mortality, with the conclusion that benefit from their use predominantly derives from BP lowering. These conclusions have since been confirmed by recent meta-analyses [1,2,217,292]. These meta-analyses have reported cause-specific differences on outcomes between some drugs (e.g. less stroke prevention with beta-blockers, and less heart failure prevention with CCBs); however, overall, major cardiovascular outcomes and mortality were similar with treatment

**Table 65.20** Compelling and possible contraindications to the use of specific antihypertensive drugs

| Drug                                                                    | Contraindications                                                                                                                                                                                                                                        |                                                                                                                                                                 |
|-------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                         | Compelling                                                                                                                                                                                                                                               | Possible                                                                                                                                                        |
| Diuretics (thiazides/thiazide-like, e.g. chlorthalidone and indapamide) | <ul style="list-style-type: none"> <li>■ Gout</li> </ul>                                                                                                                                                                                                 | <ul style="list-style-type: none"> <li>■ Metabolic syndrome</li> <li>■ Glucose intolerance</li> <li>■ Pregnancy</li> <li>■ Hypercalcaemia</li> </ul>            |
| Beta-blockers                                                           | <ul style="list-style-type: none"> <li>■ Asthma</li> <li>■ Any high-grade sinoatrial or atrioventricular block</li> <li>■ Bradycardia (heart rate &lt;60 beats/min)</li> </ul>                                                                           | <ul style="list-style-type: none"> <li>■ Metabolic syndrome</li> <li>■ Glucose intolerance</li> <li>■ Athletes and physically active patients</li> </ul>        |
| Calcium antagonists (dihydropyridines)                                  |                                                                                                                                                                                                                                                          | <ul style="list-style-type: none"> <li>■ Tachyarrhythmia</li> <li>■ Heart failure (HFrEF, class III or IV)</li> <li>■ Pre-existing severe leg oedema</li> </ul> |
| Calcium antagonists (verapamil, diltiazem)                              | <ul style="list-style-type: none"> <li>■ Any high-grade sinoatrial or atrioventricular block</li> <li>■ Severe left ventricular dysfunction (left ventricular ejection fraction &lt;40%)</li> <li>■ Bradycardia (heart rate &lt;60 beats/min)</li> </ul> | <ul style="list-style-type: none"> <li>■ Constipation</li> </ul>                                                                                                |
| ACE inhibitors                                                          | <ul style="list-style-type: none"> <li>■ Pregnancy</li> <li>■ Previous angioneurotic oedema</li> <li>■ Hyperkalaemia (potassium &gt;5.5 mmol/L)</li> <li>■ Bilateral renal artery stenosis</li> </ul>                                                    | <ul style="list-style-type: none"> <li>■ Women of child-bearing potential without reliable contraception</li> </ul>                                             |
| ARBs                                                                    | <ul style="list-style-type: none"> <li>■ Pregnancy</li> <li>■ Hyperkalaemia (potassium &gt;5.5 mmol/L)</li> <li>■ Bilateral renal artery stenosis</li> </ul>                                                                                             | <ul style="list-style-type: none"> <li>■ Women of child-bearing potential without reliable contraception</li> </ul>                                             |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HFrEF, heart failure with reduced ejection fraction.

based on initial therapy with all five major classes of treatment. These Guidelines thus recommend that the same five major classes of drugs should form the basis of antihypertensive therapy. There are compelling or possible contraindications for each class of drug (Table 65.20) and preferential use of some drugs for some conditions, as discussed below. There is also evidence that there are differences in the persistence and discontinuation rates of the major drug classes [293,294].

Other classes of drugs have been less widely studied in event-based RCTs or are known to be associated with a higher risk of adverse effects [e.g. alpha-blockers, centrally acting agents, and mineralocorticoid receptor antagonists (MRAs)]. These are useful additions to the antihypertensive armamentarium in patients whose BP cannot be controlled by proven combinations of the aforementioned major drug classes.

#### BLOCKERS OF THE RENIN-ANGIOTENSIN SYSTEM (ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS)

Both ACE inhibitors and ARBs are among the most widely used classes of antihypertensive drugs. They have similar effectiveness [295,296] as each other and other major drug classes on major cardiovascular events and mortality outcomes [2,292]. ARBs are associated with significantly lower treatment discontinuation rates for adverse events than those of all other antihypertensive therapies [297], and similar rates to placebo [294]. ACE inhibitors and ARBs should not be combined for the treatment of hypertension because there is no added benefit on outcomes and an excess of renal adverse events [298,299]. Dual combination

of RAS blockers also led to the premature cessation of another trial due to adverse events [291], when a renin inhibitor, aliskiren, was combined with either an ACE inhibitor or an ARB in people with diabetes. This result halted further research into the clinical utility of aliskiren for BP treatment.

Both ACE inhibitors and ARBs reduce albuminuria more than other BP-lowering drugs and are effective at delaying the progression of diabetic and nondiabetic CKD [217]. A recent meta-analysis shows that RAS blockers are the only antihypertensive agents for which evidence is available of a reduced risk of end-stage renal disease [217].

ACE inhibitors and ARBs also appear effective in preventing or regressing HMOD, such as LVH and small artery remodelling, for an equivalent reduction in BP [292]. Both drugs reduce incident AF, which may be related to improved left ventricular function and more effective left ventricular structural regression [292]. ACE inhibitors and ARBs are also indicated postmyocardial infarction and in patients with chronic HFrEF, which are frequent complications of hypertension.

ACE inhibitors are associated with a small increased risk of angioneurotic oedema, especially in people of black African origin and, in such patients, when RAS blockers are used, an ARB may be preferred.

#### CALCIUM CHANNEL BLOCKERS

CCBs are widely used for the treatment of hypertension and have similar effectiveness as other major drug classes on BP, major cardiovascular events, and mortality outcomes [2,292]. CCBs have a greater effect on stroke reduction than expected for the BP reduction achieved, but

may also be less effective at preventing HF<sub>rEF</sub> [2,292]. However, in antihypertensive treatment trials, emergent heart failure is the event considered. Though clinically a very relevant event, it is a difficult endpoint to quantify precisely, either because symptoms and signs are relatively nonspecific or because oedema due to CCBs may result in misdiagnosis. Comparison with diuretics may also be difficult because fluid loss may mask signs and symptoms of incipient heart failure rather than preventing it. CCBs have also been compared with other antihypertensive agents in HMOD-based trials, and are reported to be more effective than betablockers in slowing the progression of carotid atherosclerosis, and in reducing LVH and proteinuria [17].

CCBs are a heterogeneous class of agents. Most RCTs demonstrating the benefits of CCBs on outcomes have used dihydropyridines (especially amlodipine). A smaller number of RCTs have compared non-dihydropyridines (verapamil and diltiazem) with other drugs, and meta-analyses evaluating the two subclasses (vs. other drugs) have not shown substantial differences in effectiveness [292].

#### THIAZIDE/THIAZIDE-LIKE DIURETICS, EXAMPLE CHLORTHALIDONE AND INDAPAMIDE

Diuretics have remained the cornerstone of antihypertensive treatment since their introduction in the 1960s. Their effectiveness in preventing all types of cardiovascular morbidities and mortality has been confirmed in RCTs and meta-analyses [300]. Diuretics also appear to be more effective than other drug classes in preventing heart failure [292]. There has been debate about whether thiazide-like diuretics such as chlorthalidone and indapamide should be given preference over classical thiazide diuretics (e.g. hydrochlorothiazide and bendrofluazide), but their superiority on outcomes has never been tested in head-to-head RCTs. Chlorthalidone and indapamide have been used in a number of RCTs showing cardiovascular benefits, and these agents are more potent per milligram than hydrochlorothiazide in lowering BP, with a longer duration of action compared with hydrochlorothiazide and no evidence of a greater incidence of side effects [301]. Lower dose thiazide-like diuretics (typical of modern antihypertensive treatment regimens) also have more evidence from RCTs demonstrating reductions in cardiovascular events and mortality, when compared with lower dose thiazide diuretics [302]. That said, hydrochlorothiazide, alone or in combination with a potassium-sparing agent, has also been used in BP-lowering RCTs, with positive results [303]. A recent meta-analysis of placebo-controlled studies based on thiazides, chlorthalidone and indapamide reported similar effects on cardiovascular outcomes of the three types of diuretics [300]. Therefore, in the absence of evidence from direct comparator trials and recognizing that many of the approved single-pill combinations (SPCs) are based on hydrochlorothiazide (see below), we recommend that thiazides, chlorthalidone, and indapamide can all be considered suitable antihypertensive agents. Both thiazide and thiazide-like diuretics can reduce serum potassium and have a side effect profile that is less favourable than RAS blockers, which may account for their association with a higher rate of treatment discontinuation [293,300]. They also exhibit dysmetabolic effects that increase insulin resistance and the risk of new-onset diabetes. Potassium may attenuate these effects [304], and a recent study has shown that the adverse effect of thiazides

on glucose metabolism may be reduced by the addition of a potassium-sparing diuretic [305]. Both thiazides and thiazide-like agents are less effective antihypertensive agents in patients with a reduced GFR (eGFR <45 mL/min) and become ineffective when the eGFR is less than 30 mL/min. In such circumstances, loop diuretics such as furosemide (or torasemide) should replace thiazides and thiazide-like diuretics to achieve an antihypertensive effect.

#### BETA-BLOCKERS

RCTs and meta-analyses demonstrate that when compared with placebo, beta-blockers significantly reduce the risk of stroke, heart failure, and major cardiovascular events in hypertensive patients [300]. When compared with other BP-lowering drugs, beta-blockers are usually equivalent in preventing major cardiovascular events, except for less effective prevention of stroke, which has been a consistent finding [1,2,217]. It is possible that the difference originated from small differences in achieved BP (including central SBP [108] between different drug treatments), to which cerebrovascular events may be especially sensitive. RCTs based on HMOD have also indicated that beta-blockers are somewhat less effective than RAS blockers and CCBs in preventing or regressing LVH, carotid IMT, aortic stiffness, and small artery remodelling [17]. In addition, a mortality benefit in postmyocardial infarction is uncertain in patients without left ventricular dysfunction [306]. Beta-blockers, as well as diuretics, and particularly their combination, are also associated with increased risk of new-onset diabetes in predisposed subjects (mostly those with the metabolic syndrome). They also exhibit a somewhat less favourable side effect profile than that of RAS blockers, with a higher rate of treatment discontinuation when assessed in real-life conditions [293].

Beta-blockers have been shown to be particularly useful for the treatment of hypertension in specific situations such as symptomatic angina, for heart rate control, postmyocardial infarction, HF<sub>rEF</sub>, and as an alternative to ACE inhibitors or ARBs in younger hypertensive women planning pregnancy or of child-bearing potential.

Finally, beta-blockers are not a homogeneous class. In recent years, the use of vasodilating beta-blockers – such as labetalol, nebivolol, celiprolol, and carvedilol – has increased. Studies on nebivolol have shown that it has more favourable effects on central BP, aortic stiffness, endothelial dysfunction, and so on. It has no adverse effect on the risk of new-onset diabetes and a more favourable side effect profile than classical beta-blockers [307,308], including less adverse effects on sexual function. Bisoprolol, carvedilol and nebivolol have been shown to improve outcomes in RCTs in heart failure [136]; however, there are no RCTs reporting patient outcomes with these beta-blockers in hypertensive patients.

#### OTHER ANTIHYPERTENSIVE DRUGS

Centrally active drugs were widely used in the earliest decades of antihypertensive treatment when other treatments were not available, but are less frequently used now, principally because of their poorer tolerability relative to the newer major classes of drugs. The alpha-blocker doxazosin was effective in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) as third-line therapy (with no increase in the risk of heart failure) [309], and was more effective than placebo but less effective than spironolactone at lowering BP in resistant hypertension

in the Prevention And Treatment of Hypertension With Algorithm-based therapy-2 (PATHWAY-2) study [310]. Alpha-blockers may also be required in specific indications (e.g. the treatment of symptomatic prostatic hypertrophy). Antihypertensive drugs, other than the major classes already discussed above, are no longer recommended for the routine treatment of hypertension, and are primarily reserved for add-on therapy in rare cases of drug-resistant hypertension where all other treatment options have failed.

## DRUG TREATMENT STRATEGY FOR HYPERTENSION

Guidelines have generated a variety of different strategies to initiate and escalate BP-lowering medication to improve BP control rates. In previous Guidelines, the emphasis was on initial use of different monotherapies, increasing their dose, or substituting for another monotherapy. However, increasing the dose of monotherapy produces little additional BP lowering and may increase the risk of adverse effects, while switching from one monotherapy to another is frustrating, time consuming, and often ineffective. For these reasons, more recent Guidelines have increasingly focused on the stepped-care approach, initiating treatment with different monotherapies and then sequentially adding other drugs until BP control is achieved. Despite this, BP control rates have remained poor worldwide. As shown by recent observations, irrespective of the world region, whether high-income or low-income economies, or the level of sophistication of healthcare provision, only 40% of patients with hypertension are treated; of these, only 35% are controlled to a BP of less than 140/90 mmHg [12]. This failure to achieve BP control in most hypertensive patients, despite numerous iterations of previous Guidelines, suggests that these treatment strategies are not working and that a different approach is needed. This Task Force believes that one of the most important issues to address in these Guidelines is 'how do we improve BP control in treated patients?'. This has become an even more pressing matter because, based on new evidence, current Guidelines are recommending more stringent BP targets (on-treatment values of  $\leq 130/80$  mmHg in the general population and  $\leq 140/90$  mmHg in older hypertensive people), which will make the achievement of BP control even more challenging.

Several reasons need to be considered to identify why the current treatment strategy has failed to achieve better BP control rates:

1. *Efficacy of pharmacological therapies.* Are the best available treatments, in whatever combination, incapable of controlling BP in most patients? The evidence from RCTs demonstrating that BP control can be achieved in most recruited patients, and that no more than 5–10% of these patients exhibit resistance to the selected treatment regimen, suggests that ineffective drug therapy is not the source of the problem.
2. *Physician or treatment inertia.* (i.e. failure to adequately up-titrate treatment). Evidence suggests that inertia [311] contributes to suboptimal BP control, with many patients remaining on monotherapy and/or suboptimal doses, despite inadequate BP control [12].
3. *Patient adherence to treatment.* Evidence is accumulating that adherence is a much more important factor than previously recognized. Studies using urine or blood assays for the presence or absence of medication have shown that adherence to treatment is low. This is supported by studies in the general population in which adherence to treatment, based on prescription refilling, was  $<50\%$  of the treatment in half of the patients [312]. Poor adherence has also been shown to be associated with increased cardiovascular risk in various studies [313] (see section 'Patient follow-up').
4. *Insufficient use of combination treatment.* BP is a multi-regulated variable depending on many compensating pathways. Consequently, combinations of drugs, working through different mechanisms, are required to reduce BP in most people with hypertension. Thus, monotherapy is likely to be inadequate therapy in most patients. Indeed, almost all patients in RCTs have required combinations of drugs to control their BP [314].
5. *Complexity of current treatment strategies.* There is also evidence that adherence to treatment is adversely affected by the complexity of the prescribed treatment regimen. In a recent study, adherence to treatment was strongly influenced by the number of pills that a patient was prescribed for the treatment of hypertension [315]. Nonadherence was usually less than 10% with a single pill, rising to 20% with two pills, 40% with three pills, and very high rates of partial or complete nonadherence in patients receiving five or more pills [315].

The above considerations suggest that the most effective evidence-based treatment strategy to improve BP control is one that: encourages the use of combination treatment in most patients, especially in the context of lower BP targets; enables the use of SPC therapy for most patients, to improve adherence to treatment; and follows a treatment algorithm that is simple, applies to all patients, and is pragmatic, with the use of SPC therapy as initial therapy for most patients, except those with BP in the high-normal range and in frail older patients (see below).

## DRUG COMBINATIONS FOR HYPERTENSION TREATMENT

Among the large number of RCTs of antihypertensive therapy, only a few have directly compared different two-drug combinations, with systematic use of the two combinations in both arms. In other trials, treatment was initiated using monotherapy in either arm and another drug (and sometimes more than one drug) was added, usually in a nonrandomized fashion, according to a prespecified treatment algorithm. In a few trials, the design precluded the use of what might be considered optimal combinations because multiple monotherapies were being evaluated [e.g. the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), where the add-on therapy to either a diuretic, CCB, ACE inhibitor, or alpha-blocker was a beta-blocker, clonidine, or reserpine] [316].

With this caveat, Table 65.21 shows that a variety of drug combinations have been used in at least one active arm of placebo-controlled trials and have been associated with significant benefit on major cardiovascular events. In trials comparing different regimens (Table 65.22), all combinations have been used in a larger or



**Table 65.21** Major drug combinations used in trials of antihypertensive treatment in a stepped approach or as a randomized combination (combinations vs. placebo or monotherapy)

| Trial                                                                                        | Comparator                                     | Type of patients              | SBP difference (mmHg) | Outcomes [change in relative risk (%)]       |
|----------------------------------------------------------------------------------------------|------------------------------------------------|-------------------------------|-----------------------|----------------------------------------------|
| <b>ACE inhibitor and diuretic combination</b>                                                |                                                |                               |                       |                                              |
| PROGRESS [27]                                                                                | Placebo                                        | Previous stroke or TIA        | -9                    | -28% strokes ( $P < 0.001$ )                 |
| ADVANCE [229]                                                                                | Placebo                                        | Diabetes                      | -5.6                  | -9% micro/macrovacular events ( $P = 0.04$ ) |
| HYVET [220]                                                                                  | Placebo                                        | Hypertensive; $\geq 80$ years | -15                   | -34% cardiovascular events ( $P < 0.001$ )   |
| <b>ARB and diuretic combination</b>                                                          |                                                |                               |                       |                                              |
| SCOPE [330]                                                                                  | Diuretic+placebo                               | Hypertensive; $\geq 70$ years | -3.2                  | -28% nonfatal strokes ( $P = 0.04$ )         |
| <b>CCB and diuretic combination</b>                                                          |                                                |                               |                       |                                              |
| FEVER [331]                                                                                  | Diuretic+placebo                               | Hypertensive                  | -4                    | -27% cardiovascular events ( $P < 0.001$ )   |
| <b>ACE inhibitor and CCB combination</b>                                                     |                                                |                               |                       |                                              |
| Syst-Eur [332]                                                                               | Placebo                                        | Older with ISH                | -10                   | -31% cardiovascular events ( $P < 0.001$ )   |
| Syst-China [333]                                                                             | Placebo                                        | Older with ISH                | -9                    | -37% cardiovascular events ( $P < 0.004$ )   |
| <b>Beta-blocker and diuretic combination</b>                                                 |                                                |                               |                       |                                              |
| Coope and Warrender [322]                                                                    | Placebo                                        | Older hypertensive            | -18                   | -42% strokes ( $P < 0.03$ )                  |
| SHEP [323]                                                                                   | Placebo                                        | Older with ISH                | -13                   | -36% strokes ( $P < 0.001$ )                 |
| STOP-H [324]                                                                                 | Placebo                                        | Older hypertensive            | -23                   | -40% cardiovascular events ( $P = 0.003$ )   |
| STOP-H 2 [334]                                                                               | ACE inhibitor or conventional antihypertensive | Hypertensive                  | 0                     | NS difference in cardiovascular events       |
| <b>Combination of two RAS blockers/ACE inhibitor + ARB or RAS blocker + renin inhibitor)</b> |                                                |                               |                       |                                              |
| ONTARGET [299]                                                                               | ACE inhibitor or ARB                           | High-risk patients            |                       | More renal events                            |
| ALTITUDE [291]                                                                               | ACE inhibitor or ARB                           | High-risk diabetic patients   |                       | More renal events                            |

Abbreviations: ACE, angiotensin-converting enzyme; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicon – MR Controlled Evaluation; ALTITUDE, Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; FEVER, Felodipine Event Reduction; HYVET, Hypertension in the Very Elderly Trial; ISH, isolated systolic hypertension; NS, non-significant; ONTARGET, Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint trial; PROGRESS, perindopril protection against recurrent stroke study; RAS, renin-angiotensin system; SBP, systolic blood pressure; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; STOP-H, Swedish Trial in Old Patients with Hypertension; Syst-China, Systolic Hypertension in China; Syst-Eur, Systolic Hypertension in Europe; TIA, transient ischaemic attack.

smaller proportion of patients, without major differences in benefits. The only exceptions are two trials in which a large proportion of the patients received either an ARB–diuretic combination [317] or CCB–ACE inhibitor combination [318], with both regimens being superior to a beta-blocker–diuretic combination in reducing cardiovascular outcomes. However, in six other trials (with seven comparisons), beta-blockers followed by diuretics or diuretics followed by beta-blockers were not associated with a significantly different risk of any cardiovascular outcome [233,234,316,319–321], and the beta-blocker–diuretic combination was significantly more effective than placebo in three trials [322–324]. It should be mentioned that the beta-blocker–diuretic combination may result in more cases of new-onset diabetes in susceptible individuals compared with other combinations [325]. A rarely used combination of thiazide and potassium-sparing diuretic (amiloride) has also been shown to be equivalent to CCB-based treatment [310,326], and was recently reported to be associated with fewer metabolic adverse effects compared with thiazide alone (less hypokalaemia and glucose intolerance) [305].

Three outcome trials directly compared two different combinations, each involving a combination of a RAS blocker (ACE inhibitor or ARB) and a CCB with other combinations. In the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial, the ACE inhibitor–CCB combination was superior to the same ACE inhibitor in combination with a thiazide diuretic at preventing major cardiovascular outcomes, despite no apparent BP difference between the two arms [327]. This finding was not confirmed in the Combination of OLMesartan and a CCB or diuretic in Japanese older hypertensive patients (COLM) [328] and Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) trials [329], which reported no significant differences in cardiovascular events when a RAS blocker–CCB combination was compared with a RAS blocker–thiazide diuretic combination, but both of these trials had insufficient statistical power.

Based on the results of outcome RCTs and recent meta-analyses, and evidence of BP-lowering effectiveness, all five major drug classes can, in principle, be combined



**Table 65.22** Major drug combinations used in trials of antihypertensive treatment in a stepped approach or as a randomized combination (combinations vs. other combinations)

| Trial                                         | Comparator               | Type of patients               | SBP difference (mmHg) | Outcomes [change in relative risk (%)]           |
|-----------------------------------------------|--------------------------|--------------------------------|-----------------------|--------------------------------------------------|
| <b>ACE inhibitor and diuretic combination</b> |                          |                                |                       |                                                  |
| CAPPP [335]                                   | BB + diuretic            | Hypertensive                   | +3                    | +5% cardiovascular events (NS)                   |
| ACCOMPLISH [327]                              | ACE inhibitor + CCB      | Hypertensive with risk factors | +1                    | +21% cardiovascular events ( $P < 0.001$ )       |
| <b>ARB and diuretic combination</b>           |                          |                                |                       |                                                  |
| LIFE [317]                                    | BB + diuretic            | Hypertensive with LVH          | -1                    | -26% stroke ( $P < 0.001$ )                      |
| <b>CCB and diuretic combination</b>           |                          |                                |                       |                                                  |
| ELSA [336]                                    | BB + diuretic            | Hypertensive                   | 0                     | NS difference in cardiovascular events           |
| CONVINCE [233]                                | BB + diuretic            | Hypertensive with risk factors | 0                     | NS difference in cardiovascular events           |
| VALUE [337]                                   | ARB + diuretic           | High-risk hypertensive         | -2.2                  | -3% cardiovascular events ( $P = \text{NS}$ )    |
| COPE [338]                                    | CCB + BB                 | Hypertensive                   | +0.7                  | NS difference in cardiovascular events or stroke |
| <b>ACE inhibitor and CCB combination</b>      |                          |                                |                       |                                                  |
| NORDIL [339]                                  | BB + diuretic            | Hypertensive                   | +3                    | NS difference in cardiovascular events           |
| INVEST [340]                                  | BB + diuretic            | Hypertensive with CAD          | 0                     | NS difference in cardiovascular events           |
| ASCOT [318]                                   | BB + diuretic            | Hypertensive with risk factors | -3                    | -16% cardiovascular events ( $P < 0.001$ )       |
| ACCOMPLISH [327]                              | ACE inhibitor + diuretic | Hypertensive with risk factors | -1                    | -21% cardiovascular events ( $P < 0.001$ )       |
| <b>Beta-blocker and diuretic combination</b>  |                          |                                |                       |                                                  |
| CAPPP [335]                                   | ACE inhibitor + diuretic | Hypertensive                   | -3                    | -5% cardiovascular events ( $P = \text{NS}$ )    |
| LIFE [317]                                    | ARB + diuretic           | Hypertensive with LVH          | +1                    | +26% stroke ( $P < 0.001$ )                      |
| ALLHAT [316]                                  | ACE inhibitor + BB       | Hypertensive with risk factors | -2                    | NS difference in cardiovascular events           |
| ALLHAT [316]                                  | CCB + BB                 | Hypertensive with risk factors | -1                    | NS difference in cardiovascular events           |
| CONVINCE [233]                                | CCB + diuretic           | Hypertensive with risk factors | 0                     | NS difference in cardiovascular events           |
| NORDIL [339]                                  | ACE inhibitor + CCB      | Hypertensive                   | -3                    | NS difference in cardiovascular events           |
| INVEST [340]                                  | ACE inhibitor + CCB      | Hypertensive with CAD          | 0                     | NS difference in cardiovascular events           |
| ASCOT [318]                                   | ACE CCB                  | Hypertensive with risk factors | +3                    | +16% cardiovascular events ( $P < 0.001$ )       |
| <b>Beta-blocker and CCB combination</b>       |                          |                                |                       |                                                  |
| COPE [329]                                    | ARB + CCB                | Hypertensive                   | +0.8                  | NS difference in cardiovascular events or stroke |
| <b>ARB and CCB combination</b>                |                          |                                |                       |                                                  |
| COPE [329]                                    | CCB + diuretic           | Hypertensive                   | -0.7                  | NS difference in cardiovascular events or stroke |
| COPE [329]                                    | CCB + BB                 | Hypertensive                   | -0.8                  | NS difference in cardiovascular events or stroke |
| COLM [328]                                    | ARB + diuretic           | Older hypertensive             | 0                     | NS difference in cardiovascular events           |

Abbreviations: ACCOMPLISH, Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension; ACE, angiotensin-converting enzyme; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARB, angiotensin receptor blocker; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; BB, beta-blocker; CAD, coronary artery disease; CAPPP, Captopril Prevention Project; CCB, calcium channel blocker; COLM, Combination of OLMesartan and a calcium channel blocker or diuretic in Japanese elderly hypertensive patients; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular Endpoints; COPE, Combination Therapy of Hypertension to Prevent Cardiovascular Events; ELSA, European Lacidipine Study on Atherosclerosis; INVEST, International Verapamil-Trandolapril Study; LIFE, Losartan Intervention For Endpoint reduction in hypertension; LVH, left ventricular hypertrophy; NORDIL, Nordic Diltiazem; NS, non-significant; SBP, systolic blood pressure; VALUE, Valsartan Antihypertensive Long-term Use Evaluation.

with one another, except for ACE inhibitors and ARBs, whose concomitant use may lead to no additional benefit but increased adverse effects and is thus discouraged. We recommend that the treatment of hypertension should be preferentially based on combinations of an ACE inhibitor or ARB with a CCB and/or a thiazide/thiazide-like diuretic. These combinations are now widely available in a single pill and in a range of doses, facilitating simplification of treatment, flexible prescribing, and up-titration from lower to higher doses. Combination therapy that includes an ACE inhibitor or ARB with either a CCB or

thiazide/thiazide-like diuretic are complementary because both CCBs or diuretics activate the RAS, which will be counteracted by their combination with an ACE inhibitor or ARB. These combinations will also limit potential adverse effects associated with diuretic or CCB monotherapy, reducing the risk of hypokalaemia due to diuretics and reducing the prevalence of peripheral oedema due to CCBs. These combinations also ensure that the RAS is inhibited as part of the treatment strategy, which is an important consideration for many patient groups (e.g. diabetes, LVH, proteinuria).

Other combinations, such as CCB + diuretic, also have evidence from RCTs supporting their use [233,329]. These are much less widely available as SPCs and do not include blockade of the RAS, which may be desirable in many patient groups.

Beta-blockers in combination should be preferentially used when there is a specific clinical indication for their use (e.g. in patients with symptomatic angina, for patients requiring heart rate control, postmyocardial infarction, chronic HFrEF, and as an alternative to ACE inhibitors or ARBs in younger hypertensive women planning pregnancy or of child-bearing potential). SPCs of beta-blockers with an ACE inhibitor, CCB, or diuretic are available.

#### RATIONALE FOR INITIAL TWO-DRUG COMBINATION THERAPY FOR MOST PATIENTS

As discussed above and with the emphasis in these Guidelines on achieving a BP target in most patients of less than 130/80 mmHg, the majority of patients will require combination therapy. Initial combination therapy is invariably more effective at BP lowering than monotherapy, indeed even low-dose combination therapy is usually more effective than maximal dose monotherapy [341]. Furthermore, the combination of medications targeting multiple mechanisms, such as blocking the RAS as well as inducing vasodilatation and/or diuresis, reduces the heterogeneity of the BP response to initial treatment and provides a steeper dose response than is observed with escalating doses of monotherapy [342]. Finally, two-drug combinations as initial therapy have been shown to be safe and well tolerated, with no or only a small increase in the risk of hypotensive episodes [341], even when given to patients with grade 1 hypertension [343], in which adverse events leading to treatment discontinuation are infrequent [294].

Although no RCT has compared major cardiovascular outcomes between initial combination therapy and monotherapy, observational evidence suggests that the time taken to achieve BP control is an important determinant of clinical outcomes, especially in higher risk patients, with a shorter time to control associated with lower risk [344]. Furthermore, there is evidence from the more general hypertensive population that, compared with patients on initial monotherapy, those who start treatment with a two-drug combination exhibit more frequent BP control after 1 year [341,345]. This is probably because initial combination treatment is associated with a better long-term adherence to the prescribed treatment regimen [346] and because initial two-drug administration prevents therapeutic inertia (i.e. reluctance or failure to upgrade treatment from one to more drugs when BP is uncontrolled) [347]. Studies from very large hypertension cohorts in usual care have shown that initial combination treatment results in reduced treatment discontinuation and a lower risk of cardiovascular events than initial monotherapy followed by the traditional stepped-care approach [312,346]. The usual-care settings for these studies may be especially relevant to study the true impact of treatment strategies on adherence and therapeutic inertia, because this can be difficult to replicate in a conventional RCT in which the motivation of the clinical staff and patients, and the monitoring of treatment, are very different from usual care. In this regard, the outcome of these real-life studies of the impact of initial combination therapy on adherence, BP

control, and cardiovascular outcomes may be especially relevant [348].

A consideration in the current Guidelines was to persist with the current stepped-care approach to BP treatment, which has been interpreted as recommending monotherapy as initial therapy for most patients, reflecting current practice. In fact, the previous Guidelines did acknowledge the possibility of initial combination therapy for patients with grade 2 or 3 hypertension, or patients at high or very high risk. In other words, initial monotherapy was only recommended for grade 1 hypertension and low-risk or moderate-risk patients. Thus, in reality, the shift in emphasis in this new guidance is subtle. However, normalizing the concept of initiating therapy with a two-drug combination for most patients with hypertension is likely to have a major effect on clinical practice and the speed and quality of BP control. We acknowledge that some low-risk or moderate-risk patients with grade 1 hypertension may achieve their BP target with monotherapy, but this is unlikely in patients with an initial SBP more than 150 mmHg who would require a BP reduction of at least 20 mmHg. Moreover, the possibility of starting with a low-dose combination of two antihypertensive drugs, even in grade 1 hypertensive patients with low-moderate-risk, is supported by the reduction of cardiovascular events obtained by combination therapy in the upper tertile (grade 1 hypertension) in the HOPE-3 trial [212]. In patients with high-normal BP and a high cardiovascular risk or in frail older patients, treatment initiation with monotherapy may be appropriate in the former because only a small BP reduction may be required to achieve the BP target, and in the latter because in older patients baroreflex sensitivity is frequently impaired and the risk of hypotension is greater.

#### UPTITRATION OF TREATMENT TO THREE-DRUG COMBINATION THERAPY

Studies suggest that two-drug combination therapy will control BP in approximately two-thirds of patients [341]. For patients whose BP is not controlled by two-drug combination therapy, the logical option is to increase treatment to three-drug combination therapy: usually a RAS blocker, a CCB, and a diuretic. Studies suggest that a three-drug combination should control BP in more than 80% of patients [349,350]. This rate of BP control is much greater than the current rate of BP control across Europe in treated hypertensive patients. We do not recommend three-drug combinations as initial therapy.

#### RATIONALE FOR SINGLE-PILL COMBINATION THERAPY AS USUAL THERAPY FOR HYPERTENSION

The 2013 ESH/ESC Guidelines [17] favoured the use of combinations of two antihypertensive drugs in a single pill, because reducing the number of pills to be taken daily improves adherence and increases the rate of BP control [346,351]. This recommendation is endorsed by the current Guidelines. It is further supported by data from recent studies using various methods to assess adherence to treatment, including the quantification of antihypertensive drugs in urine and blood [352,353], and estimates such as pill counting or prescription refills, which, although indirect, allow the measurement of adherence on a prolonged basis, thereby accounting for its time-variable nature [347,354]. These studies have unequivocally shown a direct inverse relationship between the number of pills and the

likelihood of adherence. This approach is now facilitated by the availability of several SPCs with a range of dosages, which eliminates the often-stated disadvantage of SPC therapy (i.e. the inability to increase the dose of one drug independently of the other). It is also convenient that the most widely available SPCs mirror the major drug class combinations recommended by these Guidelines. The major advantage of an SPC as the usual therapeutic approach for hypertension is that patients can progress from 1, 2, or 3 drug treatments while remaining on a simple treatment regimen with a single pill throughout, increasing the likelihood of adherence to therapy and achieving BP control. Such an approach has the potential to double BP control rates in treated patients from the present low level of 40%. Although, at present, the availability of two-drug SPCs is largely limited to a RAS blocker with either a CCB or diuretic, it would be desirable to see the development of an expanded range of low-cost SPCs in different drug formulations, tailored to different clinical requirements.

Polypills have also emerged as SPCs (i.e. a fixed-dose combination of one or more antihypertensive agents with a statin and low-dose aspirin), with the rationale that hypertensive patients are often at sufficient cardiovascular risk to benefit from statin therapy. Studies of bioequivalence suggest that when combined in the polypill, different agents maintain all or most of their expected effect [355]. Furthermore, studies performed in the setting of secondary prevention, particularly in patients with a previous myocardial infarction, have shown that use of the polypill is accompanied by a better adherence to treatment compared with separate medications [356]. The ESC Guidelines for the management of myocardial infarction suggest that the use of the polypill may be considered to improve long-term adherence to prescribed therapy (class IIb, level B) [353]. No data are available for primary prevention in patients with hypertension. Nevertheless, the advantage of treatment simplification and adherence suggests that use of the polypill may be considered in patients with hypertension as substitution therapy, when the need and effectiveness of each polypill component has been previously established by their administration in separate tablets [355].

#### FURTHER UPTITRATION OF ANTIHYPERTENSIVE THERAPY

When BP remains uncontrolled with three-drug combination therapy, the patient is classified as having resistant hypertension, assuming that secondary causes of hypertension and poor adherence to treatment have been excluded, and that the elevation in BP has been confirmed by repeated office BP measurement, ABPM, or HBPM (see section 'Resistant hypertension'). Such patients should be considered for specialist evaluation. Additional treatment options include the addition of low-dose spironolactone (25–50 mg daily) [310] or another additional diuretic therapy [higher-dose amiloride 10–20 mg daily [357], higher dose thiazide or thiazidelike diuretics, loop diuretics in patients with significant renal impairment (eGFR <45 mL/min/m<sup>2</sup>), beta-blockers, alpha-blockers, centrally acting agents (e.g. clonidine), or, rarely, minoxidil] (see section 'Resistant hypertension').

#### THE DRUG TREATMENT ALGORITHM FOR HYPERTENSION

Reflecting on the evidence above, and recognizing the urgent need to address the factors contributing to the poor

control of BP in treated hypertensive patients (see section 'Drugs for the treatment of hypertension'), this drug treatment algorithm has been developed to provide a simple and pragmatic treatment recommendation for the treatment of hypertension, based on a few key recommendations:

1. The initiation of treatment in most patients with an SPC comprising two drugs, to improve the speed, efficiency, and predictability of BP control.
2. Preferred two-drug combinations are a RAS blocker with a CCB or a diuretic. A beta-blocker in combination with a diuretic or any drug from the other major classes is an alternative when there is a specific indication for a beta-blocker, for example angina, postmyocardial infarction, heart failure, or heart rate control.
3. Use monotherapy for low-risk patients with stage 1 hypertension whose SBP is <150 mmHg, very high-risk patients with high-normal BP, or frail older patients.
4. The use of a three-drug SPC comprising a RAS blocker, a CCB, and a diuretic if BP is not controlled by a two-drug SPC.
5. The addition of spironolactone for the treatment of resistant hypertension, unless contraindicated (see section 'Treatment of resistant hypertension').
6. The use of other classes of antihypertensive drugs in the rare circumstances in which BP is not controlled by the above treatments.
7. Information on availability and recommended doses of individual drugs, as well as SPCs and free combinations, can be found in national formularies.

This treatment algorithm focuses on the five major classes of drugs: ACE inhibitors, ARBs, CCBs, thiazide or thiazide-like diuretics, and beta-blockers. The algorithm recommends initial therapy for most patients with a two drug-combination, ideally as an SPC. Variations from the core drug treatment algorithm for uncomplicated hypertension shown in Figure 65.4 are specified in Figures 65.5–65.8. Recommended BP target ranges for treated hypertension are shown in Table 65.23.

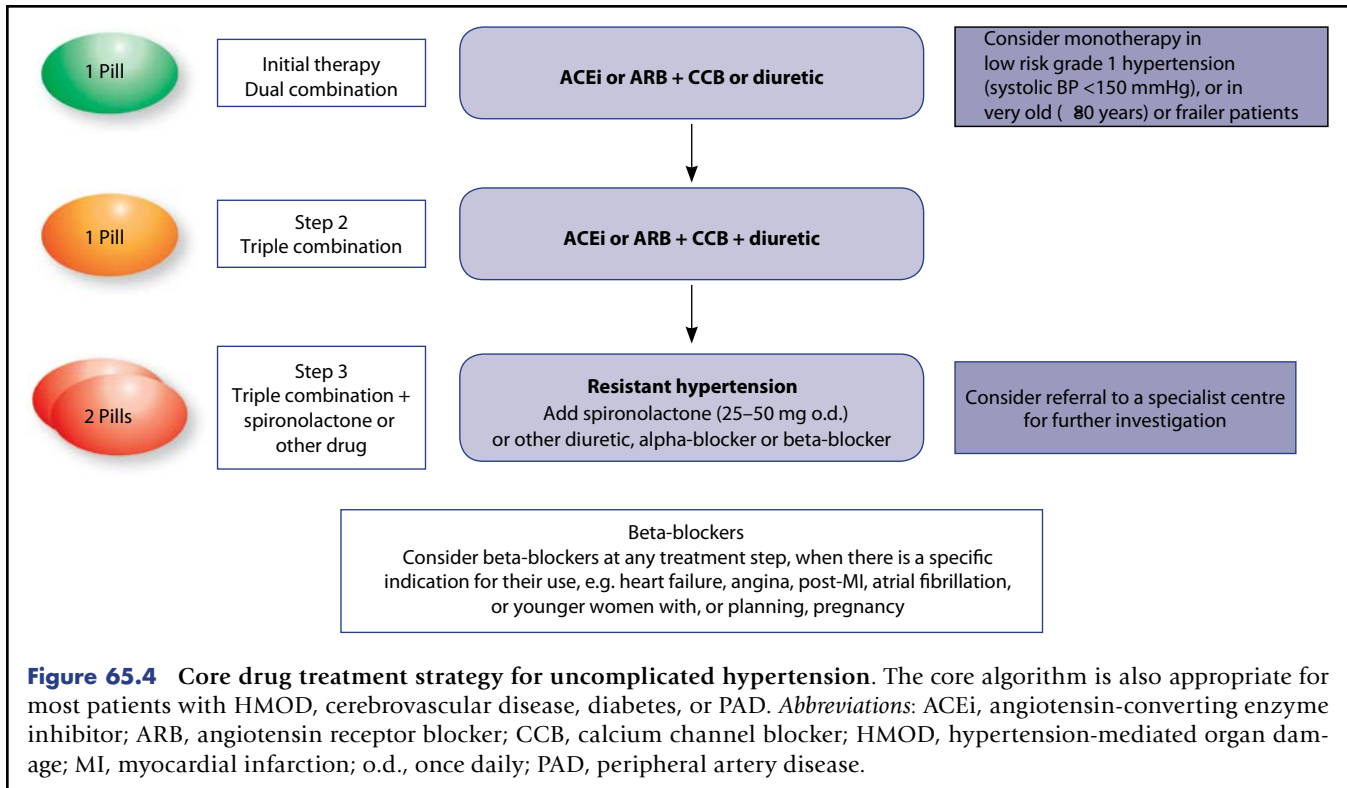
The drug treatment strategy for patients with hypertension should be based on the algorithm shown (Figures 4–8), unless there are contraindications to these drugs (Table 65.20), or concomitant conditions or diseases are present that require specific modification of the drugs, as outlined in the recommendations below.

#### DEVICE-BASED HYPERTENSION TREATMENT

Various device-based therapies have emerged, principally targeted at the treatment of resistant hypertension. These are discussed below.

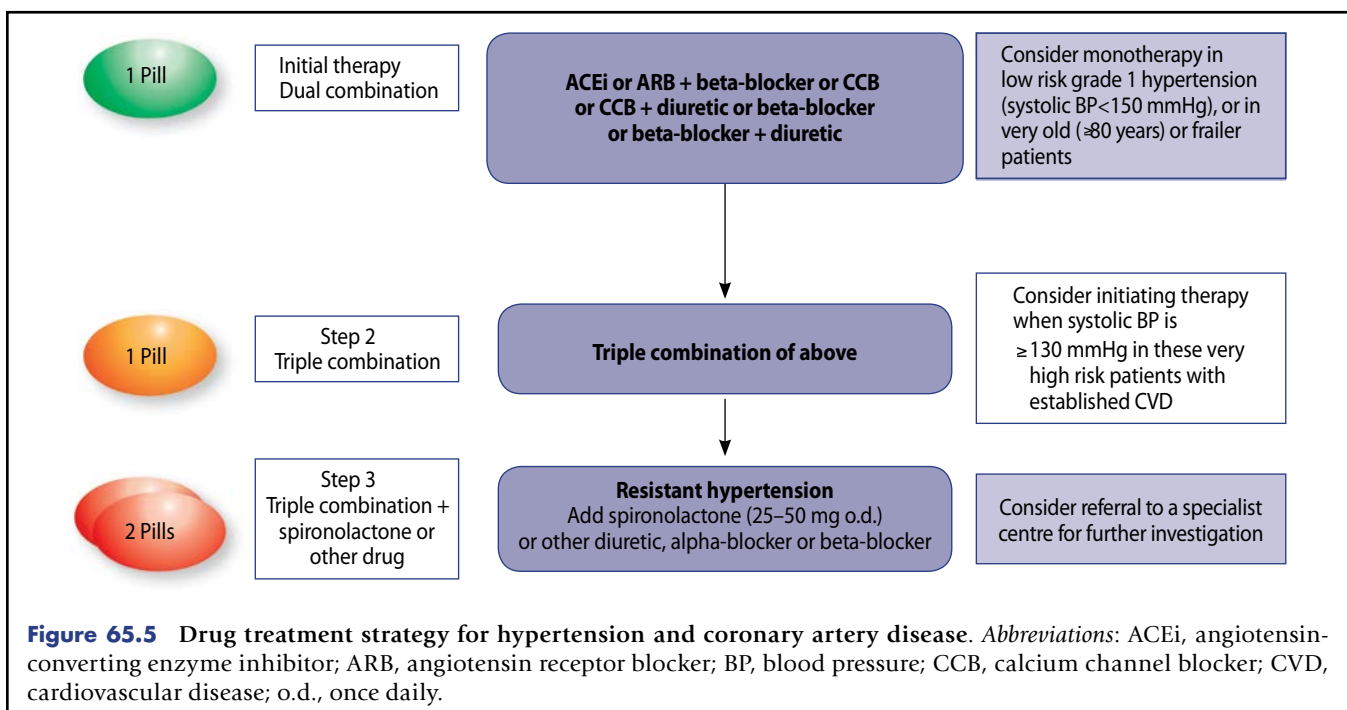
#### CAROTID BARORECEPTOR STIMULATION (PACEMAKER AND STENT)

Carotid baroreceptor stimulation or baroreflex amplification therapy – externally via an implantable pulse generator or internally via an implantable device designed to increase the strain on the carotid bulb – can lower BP in patients with resistant hypertension. An RCT with the first generation of an implantable pulse generator showed sustained



BP-lowering efficacy (and sympathetic nervous system inhibition), but with some concerns about procedural and longer-term safety [358]. A second-generation unilateral device has been developed to improve safety and sustained efficacy. A propensity score-matched comparison of the first-generation and second-generation systems revealed that BP at 12 months post-implantation was similar, with a

better safety profile for the second-generation device [359]. However, no RCT is currently available with this second-generation device. Another consideration is that implantation is costly and requires a complex surgical intervention. This has led to the development of an endovascular carotid baroreflex amplification device using a dedicated stent-like device designed to stretch the carotid bulb and increase





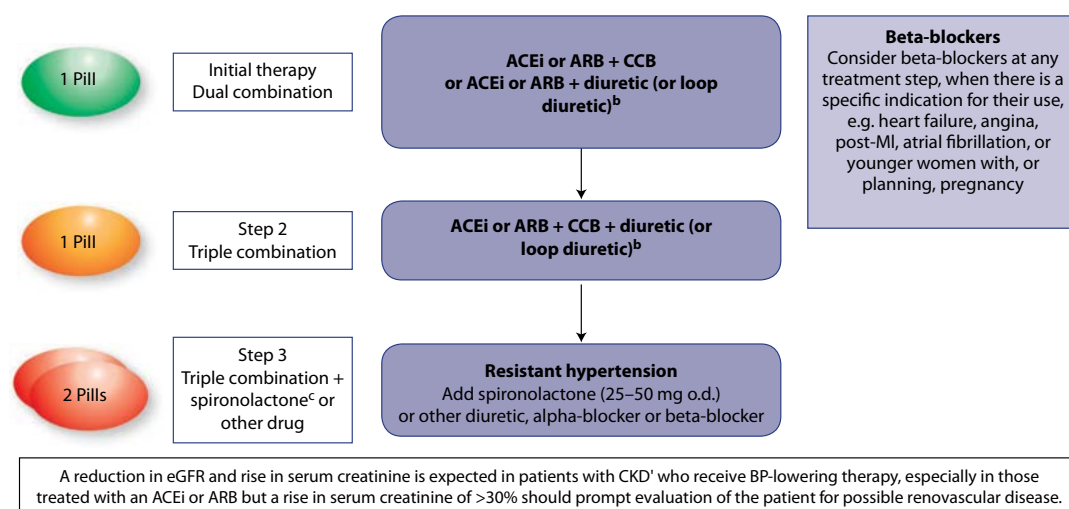


**Figure 65.6** Drug treatment strategy for hypertension and chronic kidney disease. *Abbreviations:* ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; o.d., once daily. <sup>a</sup>CKD is defined as an eGFR <60 mL/min/1.72 m<sup>2</sup> with or without proteinuria. <sup>b</sup>Use loop diuretics when eGFR is <30 mL/min/1.72 m<sup>2</sup>, because thiazide/thiazide-like diuretics are much less effective/ineffective when eGFR is reduced to this level. <sup>c</sup>Caution: risk of hyperkalaemia with spironolactone, especially when eGFR is <45 mL/min/1.72 m<sup>2</sup> or baseline K<sup>+</sup> ≥4.5 mmol/L.

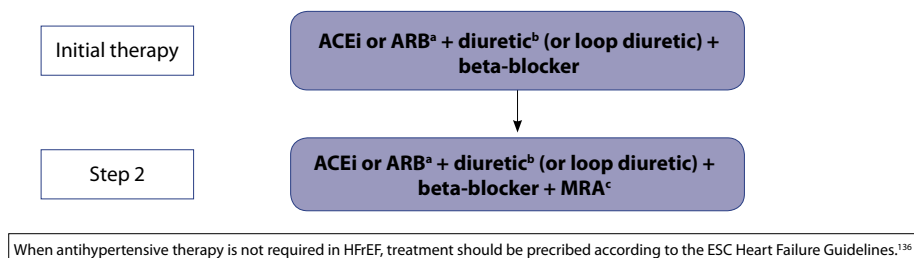


**Figure 65.7** Drug treatment strategy for hypertension and heart failure with reduced ejection fraction. Do not use non-dihydropyridine CCBs (e.g. verapamil or diltiazem). *Abbreviations:* ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; ESC, European Society of Cardiology; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist. <sup>a</sup>Consider an angiotensin receptor/neprilysin inhibitor instead of ACEi or ARB per ESC Heart Failure Guidelines [136]. <sup>b</sup>Diuretic refers to thiazide/thiazide-like diuretic. Consider a loop diuretic as an alternative in patients with oedema. <sup>c</sup>MRA (spironolactone or eplerenone). (Ponikowski P et al. *Eur Heart J* 2016; 37: 2129–2200.)[136]

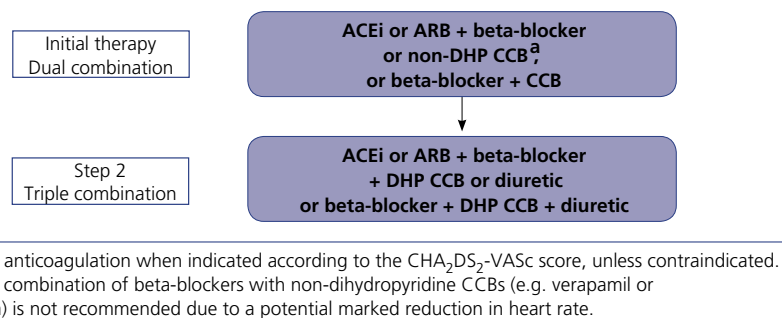


**Figure 65.8** Drug treatment strategy for hypertension and atrial fibrillation. *Abbreviations:* ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CHA<sub>2</sub>DS<sub>2</sub>-VASc, Cardiac failure, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled) – Vascular disease, Age 65–74 and Sex category (Female); DHP, dihydropyridine.



**Table 65.23** Office blood pressure treatment target range

| Age group                                | Office SBP treatment target ranges (mmHg)                 |                                                           |                                                 |                                                           |                                                           | Office DBP treatment target range (mmHg) |
|------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------------|-------------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------------|------------------------------------------|
|                                          | Hypertension                                              | + Diabetes                                                | + CKD                                           | + CAD                                                     | + Stroke <sup>a</sup> /TIA                                |                                          |
| 18–65 years                              | <b>Target to 130</b><br>or lower if tolerated<br>Not <120 | <b>Target to 130</b><br>or lower if tolerated<br>Not <120 | <b>Target to &lt;140 to 130</b><br>if tolerated | <b>Target to 130</b><br>or lower if tolerated<br>Not <120 | <b>Target to 130</b><br>or lower if tolerated<br>Not <120 | 70–79                                    |
| 65–79 years <sup>b</sup>                 | <b>Target to 130–139</b><br>if tolerated                  | <b>Target to 130–139</b><br>if tolerated                  | <b>Target to 130–139</b><br>if tolerated        | <b>Target to 130–139</b><br>if tolerated                  | <b>Target to 130–139</b><br>if tolerated                  | 70–79                                    |
| ≤80 years <sup>a</sup>                   | <b>Target to 130–139</b><br>if tolerated                  | <b>Target to 130–139</b><br>if tolerated                  | <b>Target to 130–139</b><br>if tolerated        | <b>Target to 130–139</b><br>if tolerated                  | <b>Target to 130–139</b><br>if tolerated                  | 70–79                                    |
| Office DBP treatment target range (mmHg) | 70–79                                                     | 70–79                                                     | 70–79                                           | 70–79                                                     | 70–79                                                     |                                          |

Abbreviations: AD, coronary artery disease; CKD, chronic kidney disease (includes diabetic and nondiabetic CKD); DBP, diastolic blood pressure; SBP, systolic blood pressure; TIA, transient ischaemic attack.

<sup>a</sup> Refers to patients with previous stroke and does not refer to blood pressure targets immediately after acute stroke.

<sup>b</sup> Treatment decisions and blood pressure targets may need to be modified in older patients who are frail and independent.

baroreflex stimulation. Preliminary data in humans have shown evidence of BP-lowering efficacy of this new approach [360], but data from ongoing RCTs are needed to definitively understand its longer-term efficacy and safety.

| Drug treatment strategy for hypertension                                                                                                                                                                                                                                                                                              |                    |                    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Recommendations                                                                                                                                                                                                                                                                                                                       | Class <sup>a</sup> | Level <sup>b</sup> |
| Among all antihypertensive drugs, ACE inhibitors, ARBs, beta-blockers, CCBs, and diuretics (thiazides and thiazide-like drugs such as chlorthalidone and indapamide) have demonstrated effective reduction of BP and cardiovascular events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies [2]. | <b>I</b>           | <b>A</b>           |
| Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used [233,318,327,329,341–345].                                          | <b>I</b>           | <b>A</b>           |
| It is recommended that beta-blockers are combined with any of the other major drug classes when there are specific clinical situations, e.g. angina, post-myocardial infarction, heart failure, or heart rate control [300,341].                                                                                                      | <b>I</b>           | <b>A</b>           |
| It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in an SPC. Exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is < 150 mmHg) [342,346,351].                                                                             | <b>I</b>           | <b>B</b>           |

Continued

It is recommended that if BP is not controlled<sup>c</sup> with a two-drug combination, treatment should be increased to a three-drug combination, usually a RAS blocker with a CCB and a thiazide/thiazide-like diuretic, preferably as an SPC [349,350].

**I**

**A**

It is recommended that if BP is not controlled<sup>c</sup> with a three-drug combination, treatment should be increased by the addition of spironolactone or, if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, a beta-blocker, or an alpha-blocker [310].

**I**

**B**

The combination of two RAS blockers is not recommended [291,298,299].

**III**

**A**

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; RAS, renin-angiotensin system; RCT, randomized controlled trial; SBP, systolic blood pressure; SPC, single-pill combination.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

<sup>c</sup> Adherence should be checked.

## RENAL DENERVATION

The rationale for renal denervation lays with the importance of sympathetic nervous system influences on renal vascular resistance, renin release and sodium reabsorption [361], the increased sympathetic tone to the kidney and other organs in hypertensive patients [361], and the pressor effect of renal afferent fibres documented in experimental animals [362]. Catheter-based renal denervation using radiofrequency, ultrasound, or perivascular injection of neurotoxic agents such as alcohol has been introduced as a minimally invasive treatment option for patients with resistant hypertension [363]. However, the clinical evidence in support of renal denervation as an effective

BP-lowering technique is conflicting. Several observational studies and national and international registries [364] support the BP-lowering efficacy of renal denervation originally reported in the Symplicity HTN-1 and HTN-2 trials [365]. A reduction in sympathetic activity following renal denervation has also been observed [366]. However, two RCTs with a sham procedure control [367,368] failed to document the superiority of renal denervation compared with the sham procedure in reducing BP, but did confirm the safety of the procedure. Another RCT, the Renal Denervation for Hypertension (DENERHTN) trial [369], showed the superiority of renal denervation in combination with optimized pharmacotherapy compared with pharmacotherapy alone. The PRAGUE-15 study [370] documented similar effects between renal denervation and optimized pharmacotherapy (mainly by adding spironolactone) with respect to BP-lowering efficacy; however, the latter was associated with more side effects and high discontinuation rates. Beyond resistant hypertension, interim data in the first 80 patients treated with renal denervation but with no background antihypertensive therapy showed a modest effect of renal denervation vs. sham control on 24 h ambulatory BP after 3 months [366]. This study is ongoing.

Evaluating the efficacy of renal denervation has been challenging because the procedure needs to be applied to a population with a high probability of BP response. This is complicated by the complex pathophysiology of hypertension, the lack of clinically applicable measures of sympathetic activity, the absence of predictors of the long-term BP response following renal denervation, and the absence of reliable markers of procedural success to immediately establish whether denervation has been achieved [371]. There is evidence indicating that isolated systolic hypertension, characterized by increased aortic stiffness, is associated with a limited response to renal denervation [372,373] and baroreceptor stimulation (see above). Except for rare problems related to the catheterization procedure (access site complications, vessel dissection, etc.), no major complications or deterioration of renal function have been reported.

Major uncertainties remain as to the clinical role of renal denervation outside of clinical studies, which should be performed in carefully selected patients at specialist hypertension centres and by experienced operators.

### CREATION OF AN ARTERIOVENOUS FISTULA

The central iliac arteriovenous anastomosis creates a fixed-calibre (4 mm) conduit between the external iliac artery and vein using a stent-like nitinol device (ROX arteriovenous coupler) [374,375]. Device deployment can be verified and is reversible, resulting in the diversion of arterial blood (0.8–1 L/min) into the venous circuit with immediate, verifiable reductions in BP [374,375]. The BP-lowering effect of arteriovenous anastomosis was first observed in a study of patients with chronic obstructive pulmonary disease (COPD), in whom a moderate improvement in the 6 min walking test was shown [376]. In the ROX CONTROL HTN trial, patients with resistant hypertension were randomized to receive either standard care or insertion of an arteriovenous coupler in combination with standard care [377]. At 6 months, office and ambulatory BP were significantly reduced in the coupler group compared with the control group. Some important safety aspects need to be considered. Ipsilateral venous stenosis, which needed venoplasty and/or stenting, occurred in 29% of patients.

There were no reports of right heart failure or high-output cardiac failure after device implantation over the short-term, but longer follow-up is clearly needed [377,378].

### OTHER DEVICES

The carotid body is located at the bifurcation of the common carotid. It is innervated by nerve fibres from the vagus nerve through the cervical ganglion and the carotid sinus nerve [379]. Stimulation of the carotid body drives sympathetic tone, resulting in an increase in BP and minute ventilation. Surgical resection of the carotid body is associated with reductions in BP [380] and sympathetic overactivity in patients with heart failure [381]. Devices for endovascular carotid body modification by ultrasound-guided ablation have been developed and are currently under investigation.

### Device-based therapies for hypertension

| Recommendation                                                                                                                                                                                                                          | Class <sup>a</sup> | Level <sup>b</sup> |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available [367,368]. | III                | B                  |

Abbreviation: RCT, randomized controlled trial.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

In summary, device-based therapy for hypertension is a fast-moving field. Further sham-controlled studies are needed before device-based therapies can be recommended for the routine treatment of hypertension outside of the framework of clinical trials.

## HYPERTENSION IN SPECIFIC CIRCUMSTANCES

### RESISTANT HYPERTENSION

#### DEFINITION OF RESISTANT HYPERTENSION

Hypertension is defined as resistant to treatment when the recommended treatment strategy fails to lower office SBP and DBP values to less than 140 mmHg and/or less than 90 mmHg, respectively, and the inadequate control of BP is confirmed by ABPM or HBPM in patients whose adherence to therapy has been confirmed. The recommended treatment strategy should include appropriate lifestyle measures and treatment with optimal or best tolerated doses of three or more drugs, which should include a diuretic, typically an ACE inhibitor or an ARB, and a CCB. Pseudo-resistant hypertension (see below) and secondary causes of hypertension should also have been excluded (see section 'Secondary hypertension').

Prevalence studies of resistant hypertension have been limited by variation in the definition used, and reported prevalence rates range from 5 to 30% in patients with treated hypertension. After applying a strict definition (see above) and having excluded causes of pseudo-resistant

hypertension (see section 'Pseudo-resistant hypertension'), the true prevalence of resistant hypertension is likely to be less than 10% of treated patients. Patients with resistant hypertension are at higher risk of HMOD, CKD and premature cardiovascular events [382].

### PSEUDO-RESISTANT HYPERTENSION

Several possible causes of pseudo-resistant hypertension should be evaluated and ruled out before concluding that the patient has resistant hypertension:

1. **Poor adherence to prescribed medicines** is a frequent cause of pseudo-resistant hypertension, occurring in at least 50% of patients assessed by therapeutic drug monitoring, and is directly related to the number of tablets prescribed [315] (see section 'Patient follow-up').
2. **White-coat phenomenon** (in which office BP is elevated but BP is controlled at ABPM or HBPM) is not uncommon in these patients, hence the recommendation to confirm office hypertension with ABPM or HBPM before confirming the diagnosis of resistant hypertension.
3. **Poor office BP measurement technique**, including the use of cuffs that are too small relative to the arm circumference, can result in a spurious elevation of BP.
4. **Marked brachial artery calcification**, especially in older patients with heavily calcified arteries.
5. **Clinician inertia**, resulting in inadequate doses or irrational combinations of BP-lowering drug therapies.

Other causes of resistant hypertension

1. Lifestyle factors, such as obesity or large gains in weight, excessive alcohol consumption, and high sodium intake.
2. Intake of vasopressor or sodium-retaining substances, drugs prescribed for conditions other than hypertension, some herbal remedies, or recreational drug use (cocaine, anabolic steroids, etc.) (see Table 65.24).

3. Obstructive sleep apnoea (usually, but not invariably, associated with obesity).
4. Undetected secondary forms of hypertension (see section 'Secondary hypertension').
5. Advanced HMOD, particularly CKD or large-artery stiffening.

Resistant hypertension is associated with older age (especially >75 years), male sex, black African origin, higher initial BP at diagnosis of hypertension, highest BP ever reached during the patient's lifetime, frequent outpatient visits, obesity, diabetes, atherosclerotic disease and HMOD, CKD, and a Framingham 10-year coronary risk score more than 20% [383,384].

### DIAGNOSTIC APPROACH TO RESISTANT HYPERTENSION

Diagnosis of resistant hypertension requires detailed information about:

1. The patient's history, including lifestyle characteristics, alcohol and dietary sodium intake, interfering drugs or substances, and sleep history.
2. The nature and dosing of the antihypertensive treatment.
3. A physical examination, with a particular focus on determining the presence of HMOD and signs of secondary hypertension.
4. Confirmation of treatment resistance by out-of-office BP measurements (i.e. ABPM or HBPM).
5. Laboratory tests to detect electrolyte abnormalities (hypokalaemia), associated risk factors (diabetes), organ damage (advanced renal dysfunction), and secondary hypertension.
6. Confirmation of adherence to BP-lowering therapy.

Patients should be screened for a secondary cause of hypertension, especially primary aldosteronism [386] or atherosclerotic renal artery stenosis, particularly in older patients or patients with CKD. Poor adherence to treatment should be considered, but its identification may

**Table 65.24** Resistant hypertension characteristics, secondary causes, and contributing factors

| Characteristics of patients with resistant hypertension                                                                                                                                                                                                                     | Causes of secondary resistant hypertension                                                                                                                                                                      | Drugs and substances that may cause raised BP                                                                                                                                                                                                                                                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Demographics</b> <ul style="list-style-type: none"> <li>Older age (especially &gt;75 years)</li> <li>Obesity</li> <li>More common in black people</li> <li>Excess dietary sodium intake</li> <li>High baseline BP and chronicity of uncontrolled hypertension</li> </ul> | <b>More common causes</b> <ul style="list-style-type: none"> <li>Primary hyperaldosteronism</li> <li>Atherosclerotic renovascular disease</li> <li>Sleep apnoea</li> <li>CKD</li> </ul>                         | <b>Prescribed drugs</b> <ul style="list-style-type: none"> <li>Oral contraceptives</li> <li>Sympathomimetic agents (e.g. decongestants in proprietary cold remedies)</li> <li>Nonsteroidal anti-inflammatory drugs</li> <li>Cyclosporin</li> <li>Erythropoietin</li> <li>Steroids (e.g. prednisolone and hydrocortisone)</li> <li>Some cancer therapies</li> </ul> |
| <b>Concomitant disease</b> <ul style="list-style-type: none"> <li>HMOD: LVH and/or CKD</li> <li>Diabetes</li> <li>Atherosclerotic vascular disease</li> <li>Aortic stiffening and isolated systolic hypertension</li> </ul>                                                 | <b>Uncommon causes</b> <ul style="list-style-type: none"> <li>Phaeochromocytoma</li> <li>Fibromuscular dysplasia</li> <li>Aortic coarctation</li> <li>Cushing's disease</li> <li>Hyperparathyroidism</li> </ul> | <b>Nonprescription drugs</b> <ul style="list-style-type: none"> <li>Recreational drugs (e.g. cocaine, amphetamines, and anabolic steroids)</li> <li>Excessive liquorice ingestion</li> <li>Herbal remedies (e.g. ephedra and ma huang)</li> </ul>                                                                                                                  |

Source: Adapted from Williams B. *Lancet* 2009; 374:1396–1398. [385]

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; HMOD, hypertension-mediated organ damage; LVH, left ventricular hypertrophy.

be challenging in routine clinical practice [387]. Some methods are easy to use but of limited value (e.g. standardized questionnaires), whereas others, such as drug screening of urine or blood, show considerable promise but are not yet widely available [388]. Other methods include the measurement of BP after directly observed treatment intake [389], which has been used in clinical trials [390] but may be more difficult to implement in routine clinical practice.

## TREATMENT OF RESISTANT HYPERTENSION

Effective treatment combines lifestyle changes (especially the reduction of sodium intake), discontinuation of interfering substances, and the sequential addition of antihypertensive drugs to the initial triple therapy. Ultimately, replacing all current drugs by a simpler treatment regimen using SPC treatment is recommended to reduce pill burden and improve adherence to treatment. The optimal drug treatment of resistant hypertension has been poorly studied. The most effective strategy seems to be additional diuretic treatment to decrease volume overload, together with the restriction of salt intake, particularly in patients with CKD. BP control may be improved by increasing the dose of the existing diuretic or by switching to a more potent thiazide-like diuretic (chlorthalidone or indapamide). A loop diuretic should replace thiazides/thiazide-like diuretics if the eGFR is less than 30 mL/min. Although resistant hypertension may show a BP reduction if the existing diuretic dose is further increased, most patients require the administration of additional drugs. There is growing evidence to suggest that the fourth-line treatment should involve a blockade of the biological effects of aldosterone through the use of MRAs [391] (spironolactone up to 50 mg/day), as shown in the PATHWAY 2 study [357] and supported by other studies and their meta-analysis [392–394]. Not all patients will be able to tolerate spironolactone due to antiandrogenic side effects resulting in breast tenderness or gynaecomastia (in 6%), impotence in men, and menstrual irregularities in women. Moreover, the efficacy and safety of spironolactone for the treatment of resistant hypertension has not yet been established in patients with significant renal impairment. As such, the use of spironolactone for resistant hypertension should usually be restricted to patients with an eGFR at least 45 mL/min and a plasma potassium concentration of 4.5 mmol/L. Moreover, electrolytes and eGFR should be monitored soon after initiation and at least annually thereafter. On theoretical grounds, alternative additional diuretic therapy to spironolactone (when it is not tolerated due to androgen-like side effects) could include the MRA eplerenone (50–100 mg/day). Amiloride (10–20 mg/day) has recently been shown to be as effective as spironolactone (25–50 mg daily) in reducing BP in the PATHWAY2 study [357]. It is emphasized that the same cautions about the use of these agents should be considered in patients with reduced eGFR and baseline potassium levels more than 4.5 mmol/L. The PATHWAY-2 study also evaluated bisoprolol (5–10 mg/day) or doxazosin modified release (4–8 mg/day) as alternatives to spironolactone. Neither was as effective as spironolactone, but they did reduce BP significantly vs. placebo when added to background treatment in resistant hypertension [310]. Thus, bisoprolol and doxazosin have an evidence base for the treatment

of resistant hypertension when spironolactone is contraindicated or not tolerated. Direct vasodilators, such as hydralazine or minoxidil, are infrequently used because they may cause severe fluid retention and tachycardia.

New BP-lowering drugs (nitric oxide donors, vasopressin antagonists, aldosterone synthase inhibitors, neutral endopeptidase inhibitors, and endothelin antagonists) are all under investigation [388].

## Resistant hypertension

### Recommendations

### Class<sup>a</sup>

### Level<sup>b</sup>

It is recommended that hypertension be defined as resistant to treatment (i.e. resistant hypertension) when:

- Optimal doses (or best-tolerated doses) of an appropriate therapeutic strategy, which should include a diuretic (typically an ACE inhibitor or an ARB with a CCB and a thiazide/thiazide-type diuretic), fails to lower clinic SBP and DBP values to <140 mmHg and/or <90 mmHg, respectively; and
- The inadequate control of BP has been confirmed by ABPM or HBPM; and
- After exclusion of various causes of pseudo-resistant hypertension (especially poor medication adherence) and secondary hypertension.

Recommended treatment of resistant hypertension is:

- Reinforcement of lifestyle measures, especially sodium restriction [395].
- Addition of low-dose spironolactone<sup>c</sup> to existing treatment [310,392,394].
- Or the addition of further diuretic therapy if intolerant to spironolactone, with either eplerenone,<sup>c</sup> amiloride,<sup>c</sup> a higher-dose thiazide/thiazide-like diuretic, or a loop diuretic [357].<sup>d</sup>
- Or the addition of bisoprolol or doxazosin [310].

**Abbreviations:** ABPM, ambulatory blood pressure monitoring; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; DBP, diastolic blood pressure; HBPM, home blood pressure monitoring; SBP, systolic blood pressure.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

<sup>c</sup> When spironolactone is not tolerated, replace with amiloride or eplerenone. The use of these drugs should be restricted to patients with an estimated glomerular filtration rate  $\geq 45$  mL/min and a plasma potassium concentration of  $\leq 4.5$  mmol/L, because of the risk of hyperkalaemia.

<sup>d</sup> A loop diuretic should replace thiazides/thiazide-like diuretics if the estimated glomerular filtration rate is  $<30$  mL/min.

## SECONDARY HYPERTENSION

Secondary hypertension is hypertension due to an identifiable cause, which may be treatable with an intervention specific to the cause. A high index of suspicion and early detection of secondary causes of hypertension are important because interventions may be curative, especially in younger patients [e.g. corrective surgery for aortic coarctation, renal angioplasty in younger



patients with renal artery fibromuscular dysplasia, reversal of an endocrine cause of hypertension (e.g. by removal of an adrenal adenoma), or drug treatment of a monogenic disorder affecting a specific drug-sensitive ion channel (e.g. selective use of amiloride in Liddle's syndrome)]. Interventions that treat the cause of secondary hypertension later in life are less likely to be curative (i.e. remove the need for antihypertensive medication) because longstanding hypertension results in vascular and other organ damage that sustains the elevated BP, but intervention is still important because it will often result in much better BP control with less medication.

The prevalence of secondary hypertension is reported to be 5–15% [396] of people with hypertension. Screening all hypertensive patients for secondary hypertension is not feasible or cost-effective; however, there are some general patient characteristics that suggest those more likely to have secondary hypertension and in whom screening should be considered after confirming that BP is elevated with ABPM (Table 65.25).

It is beyond the scope of these Guidelines to describe the detailed clinical management of specific causes of secondary hypertension. However, the commoner causes of secondary hypertension, clinical history, and screening tests are described in Table 65.26, and the typical age distribution of these causes of secondary hypertension is shown in Table 65.27. Review of these tables demonstrates that most screening can be undertaken with blood and urine tests, abdominal ultrasound, and echocardiography. Referral to a specialist centre is recommended for additional investigations to confirm a suspected diagnosis of secondary hypertension and for clinical management. Other causes of secondary hypertension due to drugs and substances, and rarer monogenic causes, are described below and are summarized in Tables 65.28 and 65.29.

## DRUGS AND OTHER SUBSTANCES THAT MAY CAUSE SECONDARY HYPERTENSION

Medications and other substances may cause a sufficient increase in BP to raise the suspicion of secondary hypertension [397] (Table 65.28). Consequently, a careful drug

history is important when considering a diagnosis of secondary hypertension. Moreover, other commonly used drugs such as nonsteroidal anti-inflammatory drugs or glucocorticoids can antagonize the BP-lowering effect of antihypertensive medications in patients treated for hypertension and may contribute to a loss of BP control.

## GENETIC CAUSES OF SECONDARY HYPERTENSION

Genetic causes of secondary hypertension are usually due to single-gene disorders (see section 'Genetics and hypertension') [194,195]. They are rare but important causes of secondary hypertension because identifying the cause can point to a specific drug treatment (Table 65.29) [194,195]. Common features of these genetic disorders are that they usually present with hypertension in children, adolescents, or young adults, and most monogenic disorders induce hypertension by increasing the renal tubular reabsorption of sodium. Thus, they are usually associated with a suppressed plasma renin concentration (PRC) or plasma renin activity (PRA), which is unusual in younger patients and especially those treated with antihypertensive medications (e.g. RAS blockers, CCBs, or diuretics), that would be expected to increase PRC or PRA. Thus, the finding of a suppressed PRC or PRA, especially while taking these drugs, should raise the suspicion of secondary hypertension due a salt-retaining state. Importantly, beta-blockers in particular, but also nonsteroidal anti-inflammatory drugs, alpha-methyl dopa, or clonidine, suppress PRC and PRA. These drugs should be discontinued (if clinically feasible) for at least 2 weeks before measuring PRC or PRA.

## HYPERTENSION URGENCIES AND EMERGENCIES

Hypertension emergencies are situations in which severe hypertension (grade 3) is associated with acute HMOD, which is often life-threatening and requires immediate but careful intervention to lower BP, usually with intravenous (i.v.) therapy [398]. The rate and magnitude of an increase in BP may be at least as important as the absolute level of BP in determining the magnitude of organ injury [399]. Typical presentations of a hypertension emergency are:

1. **Patients with malignant hypertension**, characterized by severe hypertension (usually grade 3) associated with funduscopic changes (flame haemorrhages and/or papilloedema), microangiopathy, and disseminated intravascular coagulation, and can be associated with encephalopathy (in about 15% of cases) [400], acute heart failure, and acute deterioration in renal function. The hallmark of this condition is small artery fibrinoid necrosis in the kidney, retina, and brain. The term 'malignant' reflects the very poor prognosis for this condition if untreated [401–404].
2. **Patients with severe hypertension associated with other clinical conditions** who are likely to require an urgent reduction of BP, for example acute aortic dissection, acute myocardial ischaemia, or acute heart failure.

**Table 65.25** Patient characteristics that should raise the suspicion of secondary hypertension

### Characteristic

- Younger patients (<40 years) with grade 2 hypertension or onset of any grade of hypertension in childhood
- Acute worsening hypertension in patients with previously documented chronically stable normotension
- Resistant hypertension (see section 'Resistant hypertension')
- Severe (grade 3) hypertension or a hypertension emergency (see section 'Hypertension urgencies and emergencies')
- Presence of extensive HMOD
- Clinical or biochemical features suggestive of endocrine causes of hypertension or CKD
- Clinical features suggestive of obstructive sleep apnoea
- Symptoms suggestive of pheochromocytoma or family history of pheochromocytoma

Abbreviations: CKD, chronic kidney disease; HMOD, hypertension-mediated organ damage.



**Table 65.26** Common causes of secondary hypertension

| Cause                                                           | Prevalence in hypertensive patients | Suggestive symptoms and signs                                                                                                                                                                                                                                 | Screening investigations                                                                                                                   |
|-----------------------------------------------------------------|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Obstructive sleep apnoea                                        | 5–10%                               | Snoring; obesity (can be present in non obese); morning headache; daytime somnolence                                                                                                                                                                          | Epworth score and ambulatory polygraphy                                                                                                    |
| Renal parenchymal disease                                       | 2–10%                               | Mostly asymptomatic; diabetes; haematuria, proteinuria, nocturia; anaemia, renal mass in adult polycystic CKD                                                                                                                                                 | Plasma creatinine and electrolytes, eGFR; urine dipstick for blood and protein, urinary albumin:creatinine ratio; renal ultrasound         |
| <b>Renovascular disease</b>                                     |                                     |                                                                                                                                                                                                                                                               |                                                                                                                                            |
| Atherosclerotic renovascular disease<br>Fibromuscular dysplasia | 1–10%                               | Older; widespread atherosclerosis (especially PAD); diabetes; smoking; recurrent flash pulmonary oedema; abdominal bruit<br>Younger; more common in women; abdominal bruit                                                                                    | Duplex renal artery Doppler or CT angiography or MR angiography                                                                            |
| <b>Endocrine causes</b>                                         |                                     |                                                                                                                                                                                                                                                               |                                                                                                                                            |
| Primary Aldosteronism                                           | 5–15%                               | Mostly asymptomatic; muscle weakness (rare)                                                                                                                                                                                                                   | Plasma aldosterone and renin, and aldosterone: renin ratio; hypokalaemia (in a minority): note hypokalaemia can depress aldosterone levels |
| Phaeochromocytoma                                               | <1%                                 | Episodic symptoms (the 5 'Ps'): paroxysmal hypertension, pounding headache, perspiration, palpitations, and pallor; labile BP; BP surges precipitated by drugs (e.g. beta-blockers, metoclopramide, sympathomimetics, opioids, and tricyclic antidepressants) | Plasma or 24 h urinary fractionated metanephrines                                                                                          |
| Cushing's syndrome                                              | <1%                                 | Moon face, central obesity, skin atrophy, striae and bruising; diabetes; chronic steroid use                                                                                                                                                                  | 24 h urinary-free cortisol                                                                                                                 |
| Thyroid disease (hyperthyroidism or hypothyroidism)             | 1–2%                                | Signs and symptoms of hyperthyroidism or hypothyroidism                                                                                                                                                                                                       | Thyroid function tests                                                                                                                     |
| Hyperparathyroidism<br>Other causes                             | <1%                                 | Hypercalcaemia, hypophosphataemia                                                                                                                                                                                                                             | Parathyroid hormone, Ca <sup>2+</sup>                                                                                                      |
| <b>Other causes</b>                                             |                                     |                                                                                                                                                                                                                                                               |                                                                                                                                            |
| Coarctation of the aorta                                        | <1%                                 | Usually detected in children or adolescence; different BP ( $\geq 20/10$ mmHg) between upper-lower extremities and/or between right-left arm and delayed radial-femoral femoral pulsation; low ABI interscapular ejection murmur; rib notching on chest X-ray | Echocardiogram                                                                                                                             |

Abbreviations: ABI, ankle-brachial index; BP, blood pressure; CKD, chronic kidney disease; CT, computed tomography; eGFR, estimated glomerular filtration rate; MR, magnetic resonance; PAD, peripheral artery disease.

3. Patients with sudden severe hypertension due to phaeochromocytoma, associated with organ damage.
4. Pregnant women with severe hypertension or pre-eclampsia (see section 'Hypertension and pregnancy').

The most common emergency symptoms will depend on the organs affected but may include headache, visual disturbances, chest pain, dyspnoea, dizziness, and other neurological deficits. In patients with hypertensive encephalopathy, the presence of somnolence, lethargy, tonic clonic seizures and cortical blindness may precede a loss of consciousness; however, focal neurological lesions are rare and should raise the suspicion of stroke.

**Acute stroke**, especially intracerebral haemorrhage, when associated with severe hypertension has often been termed a hypertension emergency, but a more cautious approach is now recommended for acute BP lowering in the emergency setting of acute stroke (see section 'Cerebrovascular disease and cognition').

The term 'hypertension urgency' has also been used to describe severe hypertension in patients presenting to the emergency department in whom there is no clinical evidence of acute HMOD [405]. Whilst these patients require BP reduction, they do not usually require admission to hospital, and BP reduction is best achieved with oral medication according to the drug treatment algorithm presented in Figure 65.4. However, these patients

**Table 65.27** Incidence and typical causes of secondary hypertension according to age

| Age group                        | Percent with underlying cause | Typical causes                                                                                                                                                                                                                                    |
|----------------------------------|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Young children (<12 years)       | 70–85                         | <ul style="list-style-type: none"> <li>Renal parenchymal disease</li> <li>Coarctation of the aorta</li> <li>Monogenic disorders</li> </ul>                                                                                                        |
| Adolescents (12–18 years)        | 10–15                         | <ul style="list-style-type: none"> <li>Renal parenchymal disease</li> <li>Coarctation of the aorta</li> <li>Monogenic disorders</li> </ul>                                                                                                        |
| Young adults (19–40 years)       | 5–10                          | <ul style="list-style-type: none"> <li>Renal parenchymal disease</li> <li>Fibromuscular dysplasia (especially in women)</li> <li>Undiagnosed monogenic disorders</li> </ul>                                                                       |
| Middle-aged adults (41–65 years) | 5–15                          | <ul style="list-style-type: none"> <li>Primary aldosteronism</li> <li>Obstructive sleep apnoea</li> <li>Cushing's syndrome</li> <li>Phaeochromocytoma</li> <li>Renal parenchymal disease</li> <li>Atherosclerotic renovascular disease</li> </ul> |
| Older adults (>65 years)         | 5–10                          | <ul style="list-style-type: none"> <li>Atherosclerotic renovascular disease</li> <li>Renal parenchymal disease</li> <li>Thyroid disease</li> </ul>                                                                                                |

will require urgent outpatient review to ensure that their BP is coming under control.

Acute and severe increases in BP can sometimes be precipitated by ingestion of sympathomimetics such as methamphetamine or cocaine. This can result in a hypertension emergency when there is evidence of acute HMOD.

It is emphasized that many patients in an emergency department with acute pain or distress may experience an acute elevation in BP that will be restored to normal when the pain and distress are relieved, rather than requiring any specific intervention to lower BP.

For patients with a suspected hypertension emergency, a diagnostic workup is shown in Table 65.30.

## ACUTE MANAGEMENT OF HYPERTENSIVE EMERGENCIES

Apart from acute BP lowering in stroke, there are no RCTs evaluating different treatment strategies for hypertensive emergencies. The key considerations in defining the treatment strategy are:

1. Establishing the target organs that are affected, whether they require any specific interventions other than BP lowering, and whether there is a precipitating cause for the acute rise in BP that might affect the treatment plan (e.g. pregnancy);
2. The recommended timescale and magnitude of BP lowering required for safe BP reduction;
3. The type of BP-lowering treatment required. With regard to drug treatment, in a hypertension emergency, i.v. treatment with a drug with a short half-life is ideal to allow careful titration of the BP response to treatment in a higher dependency clinical area with facilities for continuous hemodynamic monitoring.

Recommended drug treatments for specific hypertension emergencies [398,406] are shown in Table 65.31 and an expanded range of possible drug choices [398] is shown in Table 65.32. Rapid uncontrolled BP lowering is not recommended as this can lead to complications [397].

Although i.v. drug administration is recommended for most hypertension emergencies, oral therapy with ACE inhibitors, ARBs, or beta-blockers is sometimes very effective in malignant hypertension because the renin system is activated by renal ischaemia. However, low initial doses should be used because these patients can be very sensitive to these agents and treatment should take place in hospital. Further comprehensive details on the clinical management of hypertension emergencies are available [398].

## PROGNOSIS AND FOLLOW-UP

The survival of patients with hypertension emergencies has improved dramatically over past decades [407], but these patients remain at high risk [408,409] and should be screened for secondary hypertension (see section

**Table 65.28** Medications and other substances that may increase blood pressure

| Medication/Substance                         |                                                                                                                                                               |
|----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Oral contraceptive pill                      | Especially oestrogen containing; cause hypertension in 5% of women, usually mild but can be severe                                                            |
| Diet pills                                   | For example, phenylpropanolamine and sibutramine                                                                                                              |
| Nasal decongestants                          | For example, phenylephrine hydrochloride and naphazoline hydrochloride                                                                                        |
| Stimulant drugs                              | Amphetamine, cocaine, and ecstasy; these substances usually cause acute rather than chronic hypertension                                                      |
| Liquorice                                    | Chronic excessive liquorice use mimics hyperaldosteronism by stimulating the mineralocorticoid receptor and inhibiting cortisol metabolism                    |
| Immunosuppressive medications                | For example, cyclosporin A (tacrolimus has less effect on BP and rapamycin has almost no effect on BP) and steroids (e.g. corticosteroids and hydrocortisone) |
| Antiangiogenic cancer therapies              | Antiangiogenic drugs such as VEGF inhibitors (e.g. bevacizumab), tyrosine kinase inhibitors (e.g. sunitinib), and sorafenib have been reported to increase BP |
| Other drugs and substances that may raise BP | Anabolic steroids, erythropoietin, nonsteroidal anti-inflammatory drugs, and herbal remedies (e.g. ephedra and ma huang)                                      |

Source: Grossman A et al. Eur J Pharmacol 2015; 763: 15–22.

Abbreviations: BP, blood pressure; VEGF, vascular endothelial growth factor.

**Table 65.29** Rare genetic causes of secondary hypertension

| Condition                              | Phenotype                                                            | Mechanism and effect                                                                         |
|----------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| Liddle syndrome                        | Hypokalaemia, metabolic alkalosis, low PRA or PRC, low PAC           | Increased renal tubular ENaC activity: responds to treatment with amiloride                  |
| Apparent mineralocorticoid excess      | Hypokalaemia, metabolic alkalosis, low PRA or PRC, low PAC           | Decreased 11 $\beta$ -dehydrogenase isoenzyme 2                                              |
| Gordon syndrome                        | Hyperkalaemia, metabolic acidosis, low PRA or PRC, low PAC           | Overactivity of sodium chloride co-transporter                                               |
| Geller syndrome                        | Pregnancy-exacerbated hypertension, low PRA or PRC, low PAC          | Agonist effect of progesterone on the mineralocorticoid receptor                             |
| Glucocorticoid remediable hypertension | Hypokalaemia, metabolic alkalosis, low PRC or PRA, and increased PAC | Chimeric CYP11 $\beta$ 1 to CYP11 $\beta$ 2 gene: response to treatment with glucocorticoids |

Abbreviations: ENaC, epithelial sodium channel; PAC, plasma aldosterone concentration; PRA, plasma renin activity; PRC, plasma renin concentration.

'Secondary hypertension'). After discharge from hospital, when BP has reached a safe and stable level on oral therapy, we recommend frequent, at least monthly, visits in a specialized setting until the optimal target BP is achieved and long-term specialist follow-up thereafter.

**Table 65.30** Diagnostic workup for patients with a suspected hypertension emergency

#### Common tests for all potential causes

- Fundoscopy is a critical part of the diagnostic workup
- 12-lead ECG
- Haemoglobin, platelet count, fibrinogen
- Creatinine, eGFR, electrolytes, LDH, haptoglobin
- Urine albumin:creatinine ratio, urine microscopy for red cells, leucocytes, casts
- Pregnancy test in women of child-bearing age

#### Specific tests by indication

- Troponin, CK-MB (in suspected cardiac involvement, e.g. acute chest pain or acute heart failure) and NT-proBNP
- Chest X-ray (fluid overload)
- Echocardiography (aortic dissection, heart failure, or ischaemia)
- CT angiography of thorax and/or abdomen in suspected acute aortic disease (e.g. aortic dissection)
- CT or MRI brain (nervous system involvement)
- Renal ultrasound (renal impairment or suspected renal artery stenosis)
- Urine drug screen (suspected methamphetamine or cocaine use)

Abbreviations: CK-MB, creatinine kinase-muscle/brain; CT, computed tomography; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro-B natriuretic peptide.

## WHITE-COAT HYPERTENSION

As discussed in section 'Blood pressure measurement', white-coat hypertension is defined as an elevated office BP despite a normal out-of-office BP. White-coat hypertension may be present in many people with an increased office BP, with a maximum in grade 1 hypertension, and very old people (>50%). Compared with normotensive people, white-coat hypertension is associated with an increased prevalence of dysmetabolic risk factors and asymptomatic organ damage. It is also associated with a greater risk of developing type 2 diabetes and sustained hypertension, as well as an overall increased risk of cardiovascular events [68,410–412]. It is recommended that people with white-coat hypertension should have an accurate assessment of their cardiovascular risk profile, including a search for HMOD. Office and out-of-office BP (both home and ambulatory BP) should be measured frequently, for example no less than every 2 years. Treatment should consider lifestyle changes to reduce the elevated cardiovascular risk [85,86,89].

Whether or not patients with white-coat hypertension should receive antihypertensive drugs is unresolved. In white-coat hypertension, antihypertensive drugs have been shown to effectively and persistently lower office BP, with no concomitant reduction (indeed, even a small increase) of ambulatory BP values [413,414]. Whether these BP changes lead to cardiovascular protection has not been investigated with adequately powered outcome studies and remains unknown. However, it should be considered that people with white-coat hypertension have inevitably been well represented in trials documenting the protective effect of antihypertensive drugs [415], particularly those addressing conditions in which white-coat hypertension is more common, such as grade 1 hypertension or hypertension in older patients. In a recent subanalysis of the HYVET trial of the very old with hypertension, white-coat hypertension was reported to account for 55% of the trial population [416]. Thus, antihypertensive drug treatment cannot definitively be excluded for patients with white-coat hypertension and may be considered, in particular, in white-coat hypertensive people with a higher cardiovascular risk profile, such as those with HMOD, an uncertain out-of-office BP normality pattern (i.e. ambulatory but not home BP normality or vice versa), or a persistent office BP elevation at repeated visits [417–420]. No cardiovascular risk excess has been reported in patients in whom white-coat hypertension results from treatment-dependent normalization of out-of-office BP only [418,421]. Thus, whether this condition benefits from an uptitration of the existing drug treatment regimen (to also achieve office BP normalization) remains to be determined.

## MASKED HYPERTENSION

As reported in section 'Masked hypertension', masked hypertension is defined in people whose BP is normal in the office but elevated on out-of-office BP measurements. Such people usually have dysmetabolic risk factors and asymptomatic organ damage, which are substantially more frequent than in people who are truly normotensive [93,410–412,422]. The challenge is how to diagnose masked hypertension, because most hypertension screening programmes use office BP measurement, which is

**Table 65.31** Hypertensive emergencies requiring immediate blood pressure lowering with intravenous drug therapy

| Clinical presentation                                      | Timeline and target for BP reduction                             | First-line treatment                                       | Alternative                   |
|------------------------------------------------------------|------------------------------------------------------------------|------------------------------------------------------------|-------------------------------|
| Malignant hypertension with or without acute renal failure | Several hours<br>Reduce MAP by 20–25%                            | Labetalol<br>Nicardipine                                   | Nitroprusside<br>Urapidil     |
| Hypertensive encephalopathy                                | Immediately reduce MAP by 20–25%                                 | Labetalol, nicardipine                                     | Nitroprusside                 |
| Acute coronary event                                       | Immediately reduce SBP to <140 mmHg                              | Nitroglycerine, labetalol                                  | Urapidil                      |
| Acute cardiogenic pulmonary oedema                         | Immediately reduce SBP to <140 mmHg                              | Nitroprusside or nitroglycerine (with loop diuretic)       | Urapidil (with loop diuretic) |
| Acute aortic dissection                                    | Immediately reduce SBP to <120 mmHg<br>AND heart rate to <60 bpm | Esmolol and nitroprusside or nitroglycerine or nicardipine | Labetalol OR metoprolol       |
| Eclampsia and severe pre-eclampsia/HELLP                   | Immediately reduce SBP to <160 mmHg<br>AND DBP to <105 mmHg      | Labetalol or nicardipine and magnesium sulfate             | Consider delivery             |

Abbreviations: BP, blood pressure; bpm, beats/min; DBP, diastolic blood pressure; HELLP, haemolysis, elevated liver enzymes, and low platelets; i.v., intravenous; MAP, mean arterial pressure; SBP, systolic blood pressure.

**Table 65.32** Drug types, doses, and characteristics for treatment of hypertension emergencies

| Drug           | Onset of action | Duration of action | Dose                                                                                                                             | Contraindications                                                            | Adverse effects                         |
|----------------|-----------------|--------------------|----------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|-----------------------------------------|
| Esmolol        | 1–2 min         | 10–30 min          | 0.5–1 mg/kg i.v. bolus; 50–300 µg/kg/min i.v. infusion                                                                           | Second or third-degree AV block, systolic heart failure, asthma, bradycardia | Bradycardia                             |
| Metoprolol     | 1–2 min         | 5–8 h              | 2.5–5 mg i.v. bolus over 2 minutes; may repeat every 5 minutes to a maximum dose of 15 mg                                        | Second or third-degree AV block, systolic heart failure, asthma, bradycardia | Bradycardia                             |
| Labetalol      | 5–10 min        | 3–6 h              | 0.25–0.5 mg/kg i.v. bolus; 2–4 mg/min i.v. infusion until goal BP is reached, thereafter 5–20 mg/h                               | Second or third-degree AV block; systolic heart failure, asthma, bradycardia | Bronchoconstriction, foetal bradycardia |
| Fenoldopam     | 5–15 min        | 30–60 min          | 0.1 mg/kg/min i.v. infusion, increase every 15 min with 0.05 to 0.1 µg/kg/min increments until goal BP is reached                | Caution in glaucoma                                                          |                                         |
| Clevidipine    | 2–3 min         | 5–15 min           | 2 mg/h i.v. infusion, increase every 2 min with 2 mg/h until goal BP                                                             |                                                                              | Headache, reflex tachycardia            |
| Nicardipine    | 5–15 min        | 30–40 min          | 5–15 mg/h i.v. infusion, starting dose 5 mg/h, increase every 15–30 min with 2.5 mg until goal BP, thereafter decrease to 3 mg/h | Liver failure                                                                | Headache, reflex tachycardia            |
| Nitroglycerine | 1–5 min         | 3–5 min            | 5–200 µg/min i.v. infusion, 5 µg/min increase every 5 min                                                                        |                                                                              | Headache, reflex tachycardia            |
| Nitroprusside  | Immediate       | 1–2 min            | 0.3–10 µg/kg/min i.v. infusion, increase by 0.5 µg/kg/min every 5 min until goal BP                                              | Liver/kidney failure (relative)                                              | Cyanide intoxication                    |
| Enalaprilat    | 5–15 min        | 4–6 h              | 0.625–1.25 mg i.v. bolus                                                                                                         | History of angioedema                                                        |                                         |
| Urapidil       | 3–5 min         | 4–6 h              | 12.5–25 mg i.v. bolus; 5–40 mg/h as continuous infusion                                                                          |                                                                              |                                         |
| Clonidine      | 30 min          | 4–6 h              | 150–300 µg i.v. bolus over 5–10 min                                                                                              |                                                                              | Sedation, rebound hypertension          |
| Phentolamine   | 1–2 min         | 10–30 min          | 0.5–1 mg/kg i.v. bolus OR 50–300 µg/kg/min i.v. infusion                                                                         |                                                                              | Tachyarrhythmias, chest pain            |

Abbreviations: AV, atrioventricular; BP, blood pressure; i.v., intravenous.

normal in these people. Masked hypertension is commoner in younger rather than older individuals, and in those with an office BP in the borderline hypertension range (i.e. 130–139/80–89 mmHg). It is uncommon in people whose office BP is less than 130/80 mmHg. Masked hypertension is associated with progression to sustained office hypertension, increased frequency of developing type 2 diabetes, and the presence of HMOD. The long-term risk of fatal and nonfatal cardiovascular events approaches that of patients with sustained hypertension [68,81,93,95,423]. Patients with masked hypertension should have an accurate initial assessment of their cardiovascular risk profile. Cardiovascular risk factors (including organ damage and ideally both home and ambulatory BP) should then be periodically monitored. Factors contributing to the out-of-office BP elevation (e.g. smoking) should be discouraged and lifestyle interventions implemented to improve out-of-office BP levels. The impact of antihypertensive drug treatment on cardiovascular outcomes in people with masked hypertension has never been studied. Nevertheless, treatment with BP-lowering medication should be considered because these patients are at high cardiovascular risk, often have HMOD, and the adverse prognostic importance of out-of-office BP elevations has been well documented [68,74].

## MASKED UNCONTROLLED HYPERTENSION

MUCH occurs in some treated patients in whom the office BP appears controlled to recommended BP targets, but BP is elevated and thus uncontrolled according to out-of-office BP measurements (ABPM or HBPM) [84]. Registry-based studies in Spain have suggested that MUCH occurs in as many as 30% of treated hypertensive patients [84], and is more common with comorbidities such as diabetes and CKD and in those at highest risk. Moreover, MUCH was more commonly due to poorly controlled nocturnal rather than daytime pressures on ABPM. Presently, no data are available from outcome trials for patients with MUCH; however, mindful of their high cardiovascular risk, treatment up-titration should be considered to ensure that both office and out-of-office BP are controlled [84].

| Management of white-coat and masked hypertension                                                                                                                                                    |                    |                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Management of white-coat hypertension                                                                                                                                                               |                    |                    |
| Recommendations                                                                                                                                                                                     | Class <sup>a</sup> | Level <sup>b</sup> |
| In white-coat hypertensive patients, it is recommended to implement lifestyle changes aimed at reducing cardiovascular risk as well as regular follow-up with periodic out-of-office BP monitoring. | I                  | C                  |
| In patients with white-coat hypertension:                                                                                                                                                           | IIb                | C                  |
| ■ Drug treatment may be considered in people with evidence of HMOD or in whom cardiovascular risk is high or very high.                                                                             | III                | C                  |
| ■ Routine drug treatment is not indicated.                                                                                                                                                          |                    |                    |
| Management of masked hypertension                                                                                                                                                                   |                    |                    |

Continued

| Recommendations                                                                                                                                                                                                          |     |   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|---|
| In masked hypertension, lifestyle changes are recommended to reduce cardiovascular risk, with regular follow-up, including periodic out-of-office BP monitoring.                                                         | I   | C |
| Antihypertensive drug treatment should be considered in masked hypertension to normalize the out-of-office BP, based on the prognostic importance of out-of-office BP elevation.                                         | IIa | C |
| Antihypertensive drug up-titration should be considered in treated patients whose out-of-office BP is not controlled (i.e. masked uncontrolled hypertension), because of the high cardiovascular risk of these patients. | IIa | C |

Abbreviations: BP, blood pressure; HMOD, hypertension-mediated organ damage.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

## HYPERTENSION IN YOUNGER ADULTS (AGE <50 YEARS)

The prevalence of hypertension increases with age. Most hypertension across the age span is due to systolic hypertension; however, elevations of DBP and isolated diastolic hypertension, when they occur, are more common in younger rather than older patients [211]. There is a greater likelihood of detecting secondary hypertension in younger patients (<50 years), where the prevalence of secondary hypertension may be as high as 10% and should be considered, especially in those with more severe hypertension (see section 'Definition, classification, and epidemiological aspects of hypertension').

All younger adults with grade 2 or more severe hypertension should be offered lifestyle advice and drug treatment, as well as high-risk younger adults with grade 1 hypertension (i.e. with HMOD, CVD, diabetes, CKD, or those at high CVD risk, although cardiovascular risk is often underestimated in younger adults over shorter-term projections, such as 10 years) [35].

There is controversy about whether younger adults with uncomplicated grade 1 hypertension should be treated because of the obvious difficulty in conducting conventional clinical outcome trials in younger adults in whom the outcomes only occur after many years [424]. There is little doubt that treating stage 1 hypertension in older patients, even those at low–moderate-risk, reduces cardiovascular morbidity and mortality [425]. Moreover, long-term epidemiological studies have demonstrated a clear relationship between BP and longer-term risk of cardiovascular events and mortality in young adults with a BP more than 130/80 mmHg [424,426]. Furthermore, earlier treatment [23] can prevent more severe hypertension [427] and the development of HMOD, which may not be completely reversible with later treatment. Thus, despite the absence of RCT evidence demonstrating the benefits of antihypertensive treatment in younger adults with uncomplicated grade 1 hypertension, treatment with BP-lowering drugs may be considered prudent. If a decision is taken not to offer treatment or treatment is declined, lifestyle advice should



be prescribed, and longer-term follow-up is essential as BP will invariably rise. In younger patients with hypertension treated with BP-lowering medication, office BP should be reduced to at least 130/80 mmHg if treatment is well tolerated. Other interventions, for example statins or antiplatelet therapy, should also be considered for higher-risk patients (see section 'Should blood pressure-lowering drug treatment be initiated on the basis of blood pressure values or the level of total cardiovascular risk?').

### ISOLATED SYSTOLIC HYPERTENSION IN THE YOUNG

Some young, healthy people, and men in particular, may present with isolated grade 1 systolic hypertension (i.e. brachial SBP at least 140–159 mmHg and a normal DBP <90 mmHg), and this may be associated with a normal central aortic SBP due to excessive peripheral systolic pressure amplification [428]. It is unclear whether isolated systolic hypertension in the context of a normal aortic pressure is benign. A recent examination of prospective data from the Chicago Heart Association Detection Project found that young men with isolated systolic hypertension had a cardiovascular risk similar to that of individuals with high-normal BP and that isolated systolic hypertension in the young was closely associated with smoking [429]. On the basis of current evidence, these young individuals should receive recommendations on lifestyle modification (particularly cessation of smoking); whether they should receive drug treatment is unclear, but they do require longer-term follow-up as many will develop sustained hypertension [430].

### HYPERTENSION IN OLDER PATIENTS (AGE 65 YEARS)

The prevalence of hypertension increases with age, with a prevalence of 60% over the age of 60 years and 75% over the age of 75 years. For the purposes of these Guidelines, older is defined as at least 65 years and the very old as at least 80 years.

For many years, advanced age has been a barrier to the treatment of hypertension because of concerns about potentially poor tolerability, and even harmful effects of BP-lowering interventions in people in whom mechanisms preserving BP homeostasis and vital organ perfusion may be more frequently impaired. This approach is not appropriate, because evidence from RCTs has shown that in old and very old patients, antihypertensive treatment substantially reduces cardiovascular morbidity and cardiovascular and all-cause mortality [220,431] (see section 'Treatment of hypertension'). Moreover, treatment has been found to be generally well tolerated. However, older patients are more likely to have comorbidities such as renal impairment, atherosclerotic vascular disease, and postural hypotension, which may be worsened by BP-lowering drugs. Older patients also frequently take other medications, which may negatively interact with those used to achieve BP control. A further important caveat is that RCTs have not included very frail patients, dependent patients, and patients with postural hypotension. It is thus uncertain whether, and to what extent, such patients would benefit from BP-lowering treatment in the context of their comorbidities and reduced life expectancy. Thus, in older hypertensive patients, treatment presents more difficulties than in younger people, because the decision to treat hypertension must take into account

the patient's clinical condition, concomitant treatments, and frailty. That said, age alone must never be a barrier to treatment because high BP is an important risk factor even at the most advanced ages. Furthermore, a recent study of a cohort of older patients from the general population (thus including those with frailty) has shown that better adherence to antihypertensive treatment was associated with a reduced risk of cardiovascular events and mortality, even when age was more than 85 years (mean 90 years) [432].

It is recommended that older patients are treated according to the treatment algorithm outlined in section 'Treatment of hypertension'. In very old patients, it may be appropriate to initiate treatment with monotherapy. In all older patients, when combination therapy is used, it is recommended that this is initiated at the lowest available doses. In all older patients, and especially very old or frail patients, the possible occurrence of postural BP should be closely monitored and symptoms of possible hypotensive episodes checked by ABPM. Unless required for concomitant diseases, loop diuretics and alpha-blockers should be avoided because of their association with injurious falls [433,434]. Renal function should be frequently assessed to detect possible increases in serum creatinine and reductions in eGFR as a result of BP-related reductions in renal perfusion. When treated, BP should be lowered to a systolic value of 130–139 mmHg and a diastolic value of less than 80 mmHg if tolerated. Treated SBP values of less than 130 mmHg should be avoided. A key emphasis in treating older patients, and especially the very old, is to carefully monitor for any adverse effects or tolerability problems associated with BP-lowering treatment, keeping in mind that adverse effects can be more frequent than reported in RCTs, in which specific medical expertise and close patient supervision may minimize adverse effects and tolerability problems.

An important consideration is frail, dependent older patients, including those with orthostatic hypotension. These have been excluded from RCTs. The SPRINT trial showed the benefits of BP-lowering treatment being extended to recruited patients who were at the frailer end of the spectrum, including those with reduced gait speed [215]. This suggests that the benefit of treatment is not limited to fit and independent older patients; however, to what extent BP-lowering treatment benefits the very frail [214] and institutionalized patients remains to be determined.

In some patients, the best achievable BP may be higher than the recommended target, but it should be recognized that any amount of BP lowering is likely to be worthwhile and associated with a reduced risk of major cardiovascular events (especially stroke and heart failure) and mortality.

### WOMEN, PREGNANCY, ORAL CONTRACEPTION AND HORMONE-REPLACEMENT THERAPY

#### HYPERTENSION AND PREGNANCY

Hypertensive disorders in pregnancy affect 5–10% of pregnancies worldwide and remain a major cause of maternal, foetal, and neonatal morbidity and mortality. Maternal risks include placental abruption, stroke, multiple organ failure, and disseminated intravascular coagulation. The fetus is at high risk of intrauterine growth retardation (25% of cases of pre-eclampsia), prematurity (27% of cases of pre-eclampsia), and intrauterine death (4% of cases of pre-eclampsia) [435].

## DEFINITION AND CLASSIFICATION OF HYPERTENSION IN PREGNANCY

The definition of hypertension in pregnancy is based on office BP values, SBP at least 140 mmHg and/or DBP at least 90 mmHg [436,437], and is classified as mild (140–159/90–109 mmHg) or severe ( $\geq 160/110$  mmHg), in contrast to the conventional hypertension grading.

Hypertension in pregnancy is not a single entity but comprises:

1. **Pre-existing hypertension:** precedes pregnancy or develops before 20 weeks of gestation, and usually persists for more than 6 weeks postpartum and may be associated with proteinuria.
2. **Gestational hypertension:** develops after 20 weeks of gestation and usually resolves within 6 weeks postpartum.
3. **Pre-existing hypertension plus superimposed gestational hypertension with proteinuria.**
4. **Pre-eclampsia:** gestational hypertension with significant proteinuria ( $>0.3$  g/24 h or  $\geq 30$  mg/mmol ACR). It occurs more frequently during the first pregnancy, in multiple pregnancy, in hydatidiform mole, in antiphospholipid syndrome, or with pre-existing hypertension, renal disease, or diabetes. It is often associated with foetal growth restriction due to placental insufficiency and is a common cause of prematurity [438]. The only cure for pre-eclampsia is delivery. As proteinuria may be a late manifestation of pre-eclampsia, it should be suspected when *denovo* hypertension is accompanied by headache, visual disturbances, abdominal pain, or abnormal laboratory tests, specifically low platelets and/or abnormal liver function.
5. **Antenatally unclassifiable hypertension:** this term is used when BP is first recorded after 20 weeks of gestation and it is unclear if hypertension was pre-existing. Reassessment 6 weeks postpartum will help distinguish pre-existing from gestational hypertension.

## BLOOD PRESSURE MEASUREMENT IN PREGNANCY

BP in pregnancy should be measured in the sitting position (or the left lateral recumbent during labour) with an appropriately sized arm cuff at heart level and using Korotkoff V for DBP. Manual auscultation remains the gold standard for BP measurement in pregnancy, because automated devices tend to under-record the BP and are unreliable in severe pre-eclampsia. Only validated devices should be used in pregnancy [439]. ABPM is superior to office BP measurement for the prediction of pregnancy outcome [440]. ABPM devices recommended for use in pregnancy are more accurate than those used for office measurement or HBPM. ABPM helps avoid unnecessary treatment of white-coat hypertension, and is useful in the management of high-risk pregnant women with hypertension and those with diabetic or hypertensive nephropathy.

## INVESTIGATION OF HYPERTENSION IN PREGNANCY

Basic laboratory investigations recommended for monitoring pregnant hypertensive women include urine analysis, blood count, haematocrit, liver enzymes, serum creatinine and serum uric acid (increased in clinically evident pre-eclampsia). Hyperuricaemia in hypertensive pregnancies identifies women at increased risk of adverse maternal and foetal outcomes [441].

All pregnant women should be assessed for proteinuria in early pregnancy to detect pre-existing renal disease and, in the second half of pregnancy, to screen for pre-eclampsia. A dipstick test of at least 1+ should prompt evaluation of ACR in a single spot urine sample and a value less than 30 mg/mmol can reliably rule out proteinuria in pregnancy [442].

In addition to basic laboratory tests, the following investigations may be considered:

1. Ultrasound investigation of the kidneys and adrenals, and plasma or urinary fractionated metanephrine assays in pregnant women with a history suggestive of pheochromocytoma.
2. Doppler ultrasound of uterine arteries (performed after 20 weeks of gestation) to detect those at higher risk of gestational hypertension, pre-eclampsia, and intrauterine growth retardation [443].
3. A soluble fms-like tyrosine kinase 1:placental growth factor ratio of at least 38 can be used to exclude the development of pre-eclampsia in the next week when suspected clinically [444].

## PREVENTION OF HYPERTENSION AND PRE-ECLAMPSIA

Women at high or moderate-risk of pre-eclampsia should be advised to take 100–150 mg of aspirin daily from weeks 12–36 [445]. High risk of pre-eclampsia includes any of the following:

1. Hypertensive disease during a previous pregnancy
2. CKD
3. Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
4. Type 1 or type 2 diabetes
5. Chronic hypertension

Moderate-risk of pre-eclampsia includes one or more of the following risk factors:

1. First pregnancy
2. Age of at least 40 years
3. Pregnancy interval of more than 10 years
4. BMI of at least 35 kg/m<sup>2</sup> at first visit
5. Family history of pre-eclampsia
6. Multiple pregnancy

## CLINICAL MANAGEMENT OF HYPERTENSION IN PREGNANCY

**Mild hypertension of pregnancy (BP 140–159/90–109 mmHg)** The goal of drug treatment of hypertension in pregnancy is to reduce maternal risk; however, the agents selected must be safe for the fetus. The benefits of drug treatment for mother and fetus in hypertension in pregnancy have not been extensively studied, with the best data from a single trial using alpha-methyldopa, performed 40 years ago [446–448]. A further study suggested that tighter vs. less tight control of BP in pregnancy showed no difference in the risk of adverse perinatal outcomes and overall serious maternal complications. However, secondary analysis suggested that tighter control of BP may reduce the risk of developing more severe hypertension and pre-eclampsia [446].

Most women with pre-existing hypertension and normal renal function will not have severe hypertension and are a low risk for developing complications during pregnancy. Indeed, some of these women may be able to

withdraw their medication in the first half of pregnancy because of the physiological fall in BP. Despite the paucity of evidence, European Guidelines [17,449,450] have recommended initiating drug treatment:

1. In all women with persistent elevation of BP at least 150/95 mmHg;
2. In women with gestational hypertension (with or without proteinuria), pre-existing hypertension with the superimposition of gestational hypertension, or hypertension with subclinical HMOD, when BP is more than 140/90 mmHg.

Women with pre-existing hypertension may continue their current antihypertensive medication, but ACE inhibitors, ARBs, and direct renin inhibitors are contraindicated due to adverse foetal and neonatal outcomes. Methyldopa, labetalol, and CCBs are the drugs of choice. Beta-blockers may induce foetal bradycardia; consequently, if used, their type and dose should be carefully selected, with atenolol best avoided. Diuretic therapy is generally avoided because plasma volume is reduced in women who develop pre-eclampsia.

There are no data to define the optimal BP treatment target in pregnant women. Nevertheless, for pragmatic reasons, if treatment is initiated it is important to suggest a treatment target to calibrate how much treatment to give. A BP target of less than 140/90 is suggested for pregnant women receiving antihypertensive therapy.

**Severe hypertension of pregnancy (160/110 mmHg).** There is no agreed definition of severe hypertension, with values ranging between 160 and 180 mmHg/more than 110 mmHg. The 2018 ESC Task Force on CVD during pregnancy [435] considers an SBP of at least 170 mmHg or DBP of at least 110 mmHg an emergency in a pregnant woman, who should be immediately admitted to hospital for treatment. The selection of the antihypertensive drug and its route of administration depends on the expected time of delivery. Pharmacological treatment with i.v. labetalol, oral methyldopa, or CCB should be initiated. Intravenous hydralazine is no longer the drug of choice as it is associated with more perinatal adverse effects than other drugs [451]. However, hydralazine is still used when other treatment regimens fail to achieve adequate BP control. Intravenous urapidil can also be considered.

In hypertensive crises, that is in patients with eclampsia or severe pre-eclampsia (with or without haemolysis, elevated liver enzymes, and low platelets syndrome), hospitalization and BP-lowering therapy is essential, and delivery needs to be considered after the maternal condition has stabilized [435]. Intravenous magnesium sulfate is recommended for the prevention of eclampsia and treatment of seizures. The

consensus is to lower BP to less than 160/105 mmHg to prevent acute hypertensive complications in the mother. Both labetalol and nicardipine have shown to be safe and effective for the treatment of severe pre-eclampsia if i.v. BP-lowering therapy is necessary [452]. In both cases, monitoring of foetal heart rate is necessary. To prevent foetal bradycardia, the cumulative dose of labetalol should not exceed 800 mg/24 h. Intravenous sodium nitroprusside is contraindicated in pregnancy because of an increased risk of foetal cyanide poisoning. The drug of choice when pre-eclampsia is associated with pulmonary oedema is nitroglycerin (glyceryl trinitrate), given as an i.v. infusion of 5 µg/min, and gradually increased every 3–5 min to a maximum dose of 100 µg/min.

Delivery is indicated urgently in pre-eclampsia with visual disturbances or haemostatic disorders, and at 37 weeks in asymptomatic women [453].

**Blood pressure postpartum.** Postpartum hypertension is common in the first week. Any drug recommended can be used according to the hypertension treatment algorithm shown in Figure 65.4, with the caveats: methyldopa should be avoided because of the risk of postpartum depression and consideration should be given to drug choice in breastfeeding women.

#### HYPERTENSION AND BREASTFEEDING

All antihypertensive drugs taken by the nursing mother are excreted into breast milk. Most are present at very low concentrations except for propranolol and nifedipine, with breast milk concentrations similar to those in maternal plasma. Reference to prescribing information in breastfeeding women is important.

#### RISK OF RECURRENCE OF HYPERTENSIVE DISORDERS IN A SUBSEQUENT PREGNANCY

Women experiencing hypertension in their first pregnancy are at increased risk in a subsequent pregnancy. The earlier the onset of hypertension in the first pregnancy, the higher the risk of recurrence in a subsequent pregnancy.

#### LONG-TERM CARDIOVASCULAR CONSEQUENCES OF GESTATIONAL HYPERTENSION

Women who develop gestational hypertension or pre-eclampsia are at increased risk of hypertension, stroke, and ischaemic heart disease in later adult life [454,455]. Lifestyle modifications are indicated to avoid complications in subsequent pregnancies and to reduce maternal cardiovascular risk in the future. Therefore, annual visits to a primary care physician to check BP and metabolic factors are recommended for these patients.

Further detail on the management of hypertension and other cardiovascular disorders in pregnancy is available [435].

| Management of hypertension in pregnancy                                                                                                                                                                                                                                   |                    |                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------------|
| Recommendations                                                                                                                                                                                                                                                           | Class <sup>a</sup> | Level <sup>b</sup>    |
| In women with gestational hypertension, pre-existing hypertension superimposed by gestational hypertension, or with hypertension and subclinical organ damage or symptoms, initiation of drug treatment is recommended when SBP is $\geq 140$ mmHg or DBP $\geq 90$ mmHg. | I                  | C                     |
| In all other cases, initiation of drug treatment is recommended when SBP is $\geq 150$ mmHg or DBP is $\geq 95$ mmHg.                                                                                                                                                     | I                  | C                     |
| Methyldopa, labetalol, and CCBs are recommended as the drugs of choice for the treatment of hypertension in pregnancy [447,448].                                                                                                                                          | I                  | B (methyldopa)        |
|                                                                                                                                                                                                                                                                           | I                  | C (labetalol or CCBs) |

Continued

|                                                                                                                                        |     |   |
|----------------------------------------------------------------------------------------------------------------------------------------|-----|---|
| ACE inhibitors, ARBs, or direct renin inhibitors are not recommended during pregnancy.                                                 | III | C |
| SBP $\geq 170$ mmHg or DBP $\geq 110$ mmHg in a pregnant woman is an emergency, and admission to hospital is recommended.              | I   | C |
| In severe hypertension, drug treatment with i.v. labetalol, oral methyldopa, or nifedipine is recommended.                             | I   | C |
| The recommended treatment for hypertensive crisis is i.v. labetalol or nicardipine and magnesium.                                      | I   | C |
| In pre-eclampsia associated with pulmonary oedema, nitroglycerin given as an i.v. infusion is recommended.                             | I   | C |
| In women with gestational hypertension or mild pre-eclampsia, delivery is recommended at 37 weeks [453].                               | I   | B |
| It is recommended to expedite delivery in pre-eclampsia with adverse conditions, such as visual disturbances or haemostatic disorders. | I   | C |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; i.v., intravenous; SBP, systolic blood pressure.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

## ORAL CONTRACEPTIVE PILLS AND HYPERTENSION

Combined oestrogen–progesterone oral contraceptive pills can be associated with a small but significant increase in BP and the development of hypertension in about 5% of users [456,457]. BP usually decreases promptly following cessation of these pills; consequently, BP should be monitored before and during oral contraceptive pill treatment. The rise in BP appears to be related to the oestrogen content and may be less likely with the progestogen-only oral contraceptive pill. Older studies have demonstrated a relationship between the oral contraceptive pill and venous thrombosis and venous thromboembolism, and, to a lesser extent, myocardial infarction (especially with concomitant smoking history) and stroke [458]. More recent studies with newer-generation oral contraceptive pills have reported conflicting results. Thus, the use of oral contraceptives should consider the risks and benefits for the individual patient. Changes in BP should be carefully evaluated with follow-up readings [459]. Concomitant cardiovascular risk factors (e.g. smoking history) should be assessed and oral contraceptive pill use is not recommended if BP is elevated. In such patients, alternative forms of contraception should be offered. Discontinuation of combined oestrogen–progestin oral contraceptives in women with hypertension may improve their BP control [460].

## HORMONE-REPLACEMENT THERAPY AND HYPERTENSION

Cross-sectional studies have long established that menopause doubles the risk of developing hypertension, even after adjusting for factors such as age and BMI [461]. Although hormone-replacement therapy contains oestrogens, there is no convincing evidence that significant rises in BP will occur in otherwise normotensive menopausal women due to this therapy, or that BP will increase further due to hormone-replacement therapy in menopausal hypertensive women [462]. Hormone-replacement therapy and selective oestrogen receptor modulators should not be used for primary or secondary prevention of CVD. In summary, current evidence suggests that the use of hormone-replacement therapy is not associated with an increase in BP. Moreover, it is not contraindicated in women with hypertension, and women with hypertension may be prescribed hormone-replacement therapy as long as BP levels can be controlled by antihypertensive medication.

## HYPERTENSION IN DIFFERENT ETHNIC GROUPS

In comparison with the nonblack population, hypertension is more prevalent in the black population living in Europe [463], similarly to that reported for the USA [464]. As for the European white population, the black European population is heterogenous in nature [463], although in almost all European countries the largest ethnic group originates from the Sub-Saharan African region [463]. Hypertension epidemiology, diagnosis, and treatment have been thoroughly studied in black (i.e. Afro-American) US patients [464], in contrast to the much scarcer database available for European black people, and thus we extrapolate from US data. However, this extrapolation requires some caution as differences between the North American and the European black population exist, especially with regard to socioeconomic status, cardiovascular risk [465,466], and the response to antihypertensive drug treatment [467]. BP-related HMOD, as well as cardiovascular and renal complications, are more common and severe in black patients compared with age-matched white patients at any BP level [464]. Black hypertensive patients exhibit a similar proportional reduction of cardiovascular and renal events in response to BP-lowering treatment as white patients, with somewhat different treatment modalities. However, to achieve an effective BP reduction and BP control, salt restriction is particularly important in black patients, in whom it may lead to greater BP falls and more favourably impact on the effectiveness of BP-lowering drug treatment [468]. Hypertensive black patients also show a reduced antihypertensive response to RAS-blocker monotherapy, whereas they usually respond more effectively to thiazide or thiazide-like diuretics and CCBs [316,469,470], which in black patients may be combined with each other or with a RAS blocker, making the latter more effective. Angioedema appears more common with ACE inhibitors in black patients, which may favour the preferred use of ARBs in this population. Despite some progress in recent years, data on hypertension prevalence, management, and control in European black patients (and in other immigrant populations such as European individuals from South Asia) are still scarce [463,471], which makes this field an important area for future research. There is no evidence that the BP response to treatment in other ethnic groups differs from that reported in the general population in Europe.



| Hypertension in ethnic groups                                                                                                                                 |                    |                    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Recommendations                                                                                                                                               | Class <sup>a</sup> | Level <sup>b</sup> |
| It is recommended that a two-drug combination, usually as an SPC, is used as initial therapy for most black patients. <sup>c</sup>                            | <b>I</b>           | <b>C</b>           |
| In black patients, initial antihypertensive treatment should include a diuretic or a CCB, either in combination or with a RAS blocker [316,469]. <sup>d</sup> | <b>I</b>           | <b>B</b>           |
| In other ethnic groups, BP-lowering treatment may be based on the core treatment algorithm (see Figure 65.4).                                                 | <b>IIb</b>         | <b>C</b>           |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; RAS, renin-angiotensin system; SPC, single-pill combination.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

<sup>c</sup> Except in patients with low grade 1 hypertension or frail older patients, in whom initial treatment with a single drug may be more appropriate.

<sup>d</sup> Angioedema is more common with ACE inhibitors and thus ARBs may be preferred.

## HYPERTENSION IN DIABETES MELLITUS

High BP is a common feature of type 1 and, particularly, type 2 diabetes. Moreover, masked hypertension and a blunted nocturnal fall in BP are not infrequent in people with diabetes [472]. Recording 24 h ABPM in apparently normotensive people with diabetes may be a useful diagnostic procedure, especially in those with HMOD. Substantial evidence supports the benefits of BP reduction in people with diabetes to reduce major macrovascular and microvascular complications of diabetes, as well as reducing mortality. Proven benefits of BP lowering treatment in diabetes also include a significant reduction in the rate of end-stage renal disease [231,235], retinopathy [1], and albuminuria [1]. Diabetic neuropathy has never been included as an outcome in RCTs of BP lowering treatment.

When considering treatment for hypertension, it is important to exclude significant postural hypotension, which can be marked in people with diabetes due to autonomic neuropathy [235]. Initiation of antihypertensive drug therapy is recommended when the office BP is more than 140/90 mmHg. Alongside lifestyle interventions, treatment should usually be initiated with a twodrug combination of an ACE inhibitor or ARB with a CCB or thiazide/thiazide-like diuretic, and treatment escalated according to the recommended treatment algorithm (see section 'Treatment of hypertension'). This approach ensures that the treatment strategy includes an ACE inhibitor or ARB, which has been shown to reduce albuminuria and the appearance or progression of diabetic nephropathy more effectively than other drug classes [235]. Combination of an ACE inhibitor with an ARB is contraindicated because it is accompanied by an excess of renal adverse events [298,473,474].

Recent RCTs have shown that some antidiabetic agents (the selective inhibitors of sodium glucose cotransporter 2 in the kidney) can reduce office and ambulatory BP by several mmHg [475,476], and that this occurs even when people are treated with antihypertensive drugs. This may help improve BP control (see below), which is especially difficult in diabetes [477], and may reduce the progression

of CKD [478–481] (see also section 'Pseudo-resistant hypertension').

There has been considerable debate about the target BP that should be achieved in people with diabetes (see section 'Treatment of hypertension'). We recommend that in people with diabetes, the first objective should be to lower BP to less than 140/80 mmHg, aiming at an SBP of 130 mmHg. Provided that the treatment is well tolerated, treated SBP values of less than 130 mmHg should be considered because of the benefits on stroke prevention. Achieved SBP values of less than 120 mmHg should always be avoided. BP targets for renoprotection for patients with diabetic kidney disease are discussed in section 'Pseudo-resistant hypertension'.

| Treatment strategies in people with diabetes                                                                                                        |                    |                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Recommendations                                                                                                                                     | Class <sup>a</sup> | Level <sup>b</sup> |
| Antihypertensive drug treatment is recommended for people with diabetes when office BP is $\geq 140/90$ mmHg [1,226,235,482].                       | <b>I</b>           | <b>A</b>           |
| In people with diabetes receiving BP-lowering drugs it is recommended:                                                                              | <b>I</b>           | <b>A</b>           |
| ■ To target SBP to 130 mmHg and $<130$ mmHg if tolerated, but not $<120$ mmHg [1,231,235].                                                          | <b>I</b>           | <b>A</b>           |
| ■ In older people (aged $\geq 65$ years aged), to target to an SBP range of 130–139 mmHg [1,205,235].                                               | <b>I</b>           | <b>C</b>           |
| ■ To target the DBP to $<80$ mmHg, but not $<70$ mmHg.                                                                                              |                    |                    |
| It is recommended to initiate treatment with a combination of a RAS blocker with a CCB or thiazide/thiazide-like diuretic [1,175,205]. <sup>c</sup> | <b>I</b>           | <b>A</b>           |
| Simultaneous administration of two RAS blockers, e.g. an ACE inhibitor and ARB, is not indicated [291,298,299].                                     | <b>III</b>         | <b>A</b>           |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; RAS, renin-angiotensin system; SBP, systolic blood pressure.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

<sup>c</sup> When eGFR  $<30$  mL/min/1.73 m<sup>2</sup>, avoid thiazide/thiazide-like diuretics and consider using a loop diuretic when a diuretic is required.

## HYPERTENSION AND CHRONIC KIDNEY DISEASE

Hypertension is a major risk factor for the development and progression of CKD, irrespective of the cause of CKD. In patients with CKD, resistant hypertension, masked hypertension, and elevated nighttime BP are common, and are associated with a lower eGFR, higher levels of albuminuria, and HMOD [483,484].

The effects of lowering BP in patients with CKD have been the subject of many meta-analyses. A recent meta-analysis has shown that BP lowering significantly reduced end-stage renal disease in patients with CKD, but only in those with albuminuria and without any beneficial effect on cardiovascular events [203]. However, a more recent and larger meta-analysis has shown a significant reduction in all-cause mortality following BP reduction in patients with CKD [485].



Reduction of albuminuria has also been considered as a therapeutic target. Analyses of data from RCTs have reported that changes in urinary albumin excretion are predictors of renal and cardiovascular events [186,486]. However, there are also studies in which treatment that was less effective at reducing albuminuria was more effective at reducing cardiovascular events [175] and vice versa [176,291]. Thus, whether reducing albuminuria per se is a proxy for CVD prevention remains unresolved.

Patients with CKD should receive lifestyle advice, especially sodium restriction, and drug treatment when their office BP is more than 140/90 mmHg. Achieving recommended BP targets in CKD usually requires combination therapy, which should be initiated as a combination of a RAS blocker with a CCB or diuretic in these patients. The combination of two RAS blockers is not recommended [291]. Loop diuretics should replace thiazide diuretics when the estimated GFR is less than 30 mL/min/1.73 m<sup>2</sup>.

The evidence with respect to BP targets in patients with CKD is complex. In patients with nondiabetic CKD, one meta-analysis showed that the slowest progression on CKD was obtained with a treated SBP in the range of 110–119 mmHg in patients with albuminuria more than 1 g/day [487]. In contrast, in patients with a proteinuria less than 1 g/day, the lowest risk of developing CKD (not cardiovascular risk) was obtained with an SBP of less than 140 mmHg [487]. Another systematic review failed to demonstrate that a BP target of less than 130/80 mmHg improved clinical outcomes more than a target of less than 140/90 mmHg in nondiabetic CKD [488]. In a large retrospective cohort containing 398 419 treated hypertensive patients (30% with diabetes), the nadir SBP and DBP for the lowest risk of end-stage renal disease and mortality were 137 and 71 mmHg, respectively, with a clear increase in mortality risk at SBP less than 120 mmHg [489].

Current evidence suggests that in patients with CKD, BP should be lowered to less than 140/90 mmHg and towards 130/80 mmHg. Lifestyle advice, especially sodium restriction, may be especially effective at aiding BP lowering in patients with CKD. Because BP lowering reduces renal perfusion pressure, it is expected and not unusual for eGFR to be reduced by 10–20% in patients treated for hypertension. Thus, careful monitoring of blood electrolytes and eGFR is essential, but clinicians should not be alarmed by the anticipated decline in GFR when treatment is initiated. This decline usually occurs within the first few weeks of treatment and stabilizes thereafter. If the decline in GFR continues or is more severe, the treatment should be stopped, and the patient investigated to determine the presence of renovascular disease.

| Therapeutic strategies for treatment of hypertension in CKD                                                                                                                       |                    |                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Recommendations                                                                                                                                                                   | Class <sup>a</sup> | Level <sup>b</sup> |
| In patients with diabetic or non-diabetic CKD, it is recommended that an office BP of $\geq 140/90$ mmHg be treated with lifestyle advice and BP-lowering medication [9,203,485]. | I                  | A                  |

Continued

|                                                                                                                                                                                                                                                            |     |   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|---|
| In patients with diabetic or non-diabetic CKD:<br>■ It is recommended to lower SBP to a range of 130–139 mmHg [9,487,489].<br>■ Individualized treatment should be considered according to its tolerability and impact on renal function and electrolytes. | I   | A |
|                                                                                                                                                                                                                                                            | Ila | C |
| RAS blockers are more effective at reducing albuminuria than other antihypertensive agents, and are recommended as part of the treatment strategy in hypertensive patients in the presence of microalbuminuria or proteinuria [487,489].                   | I   | A |
| A combination of a RAS blocker with a CCB or a diuretic <sup>c</sup> is recommended as initial therapy [175].                                                                                                                                              | I   | A |
| A combination of two RAS blockers is not recommended [298].                                                                                                                                                                                                | III | A |

Abbreviations: BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAS, renin-angiotensin system; SBP, systolic blood pressure.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

<sup>c</sup> In case of eGFR  $<30$  mL/min/1.73 m<sup>2</sup>, avoid thiazide/thiazide-like diuretics and consider using a loop diuretic if required.

## HYPERTENSION AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Hypertension is the most frequent comorbidity in patients with COPD, and coincidence of the two diseases may affect 2.5% of the adult population [490]. Patients with hypertension and COPD are at particularly high cardiovascular risk [490,491]. Both conditions share similar environmental risks and, in addition, hypoxia may exacerbate the risk [490,491]. Treatment of COPD with anticholinergic agents and long-acting beta-2 adrenoceptor agonists may adversely affect the cardiovascular system (increase heart rate and BP). The presence of COPD also has an impact on the selection of antihypertensive drugs, which should consider their effects on pulmonary function. Concern has been predominantly directed to the use of beta-blockers, although there is evidence that in COPD these drugs maintain their cardiovascular-protective effects [492,493]. Beta-blockers may negatively affect the reduced basal lung function in patients with COPD, diminish the effectiveness of emergency beta-agonist administration, reduce the benefit of long-acting beta-agonist treatment, and make the discrimination of asthma and COPD more difficult. That said, when tolerated, the use of cardiac beta 1-selective beta-blockers in patients with COPD has proven to be safe in different settings, including hypertension [494]. It should also be noted that diuretics may decrease the plasma level of potassium (in addition to the hypokalaemic effects of glucocorticoids and beta 2-adrenoceptor agonists), worsen carbon dioxide retention (including metabolic alkalosis-related hypoxia in hypoventilated patients), increase haematocrit, and deteriorate mucus secretion in bronchi. Therefore, in general, diuretics are not recommended for widespread use in hypertensive patients with COPD [490,495].

In conclusion, management of hypertensive patients with COPD should include lifestyle changes, among

which cessation of smoking is essential. CCBs, ARBs or ACEIs, or the CCB/RAS blocker combination are recommended as the initial drugs of choice. If the BP response is poor, or depending on other comorbidities, thiazides or thiazide-like diuretics and beta1-selective beta-blockers can be considered.

## HYPERTENSION AND HEART DISEASE

### CORONARY ARTERY DISEASE

There are strong epidemiological relationships between CAD and hypertension. The INTERHEART study showed that 50% of the population-attributable risk of a myocardial infarction can be accounted for by lipids, with hypertension accounting for 25% [10]. Another registry-based study of over 1 million patients showed that ischaemic heart disease (angina and myocardial infarction) accounted for most (43%) of the CVD-free years of life lost due to hypertension from the age of 30 years [7].

More compelling is the beneficial effect of BP treatment on reducing the risk of myocardial infarction. A recent meta-analysis of RCTs of antihypertensive therapy showed that for every 10 mmHg reduction in SBP, CAD was reduced by 17% [2]. A similar risk reduction has been reported by others with more intensive BP control [496]. The benefits of reducing cardiac events are also evident in high-risk groups, such as those with diabetes [231,425].

There remains some inconsistency over the optimal BP target in less than patients with overt CAD, and especially whether there is a J-curve relationship between achieved BP and cardiovascular outcomes in CAD [497–500]. A recent analysis [501] of 22–672 patients with stable CAD who were treated for hypertension found that, after a median follow-up of 5.0 years, an SBP of at least 140 mmHg and a DBP of at least 80 mmHg were each associated with increased risk of cardiovascular events. An SBP of less than 120 mmHg was also associated with increased risk, as was a DBP of less than 70 mmHg. Similar findings were also reported from another analysis of RCT data evaluating the relationships between achieved BP and risks of cardiovascular outcomes [222]. Whether a J-curve phenomenon exists in patients with CAD who have been revascularized remains uncertain. Other analyses do not support the existence of a J-curve, even in hypertensive patients at increased cardiovascular risk [239]. For example, in patients with CAD and initially free from congestive heart failure enrolled in ONTARGET, a BP reduction from baseline over the examined BP range had little effect on the risk of myocardial infarction and predicted a lower risk of stroke [502]. Thus, a target BP of approximately less than 130/80 mmHg in patients with CAD appears safe and can be recommended, but achieving a BP less than 120/80 mmHg is not recommended.

#### Therapeutic strategies in hypertensive patients with CAD

| Recommendations                                                      | Class <sup>a</sup> | Level <sup>b</sup> |
|----------------------------------------------------------------------|--------------------|--------------------|
| In patients with CAD receiving BP-lowering drugs, it is recommended: |                    |                    |

|                                                                                                                                                                                                                                                                                                                                                                        |   |   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|---|
| <ul style="list-style-type: none"> <li>■ To target SBP to <math>\leq 130</math> mmHg if tolerated, but not <math>&lt; 120</math> mmHg [2,496].</li> <li>■ In older patients (aged <math>\geq 65</math> years), to target to an SBP range of 130–140 mmHg [2,496].</li> <li>■ To target DBP to <math>&lt; 80</math> mmHg, but not <math>&lt; 70</math> mmHg.</li> </ul> | I | A |
|                                                                                                                                                                                                                                                                                                                                                                        | I | A |
|                                                                                                                                                                                                                                                                                                                                                                        | I | C |
| In hypertensive patients with a history of myocardial infarction, beta-blockers and RAS blockers are recommended as part of treatment [503].                                                                                                                                                                                                                           | I | A |
| In patients with symptomatic angina, beta-blockers and/or CCBs are recommended [503].                                                                                                                                                                                                                                                                                  | I | A |

Abbreviations: BP, blood pressure; CAD, coronary artery disease; CCB, calcium channel blocker; DBP, diastolic blood pressure; RAS, renin-angiotensin system; SBP, systolic blood pressure.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

In hypertensive patients with CAD, beta-blockers and RAS blockers may improve outcomes in postmyocardial infarction [503]. In patients with symptomatic angina, beta-blockers and calcium antagonists are the preferred components of the drug treatment strategy.

### LEFT VENTRICULAR HYPERTROPHY AND HEART FAILURE

Hypertension is the leading risk factor for the development of heart failure [7], and most patients with heart failure will have a history of hypertension. This may be a consequence of CAD, which results in HFrEF. Hypertension also causes LVH, which impairs left ventricular relaxation (so-called diastolic dysfunction) and is a potent predictor of heart failure, even when left ventricular systolic function is normal and there is no preceding myocardial infarction (HFpEF). Hypertension-dependent fibrosis and structural alteration of large and small arteries (microvascular disease) also contribute.

Treating hypertension has a major impact on reducing the risk of incident heart failure and heart failure hospitalization, especially in old and very old patients [51,213,316]. This has been observed using diuretics, beta-blockers, ACE inhibitors, or ARBs, with CCBs being less effective in comparative trials [504].

Reducing BP can also lead to the regression of LVH, which has been shown to be accompanied by a reduction of cardiovascular events and mortality [125]. The magnitude of LVH regression is associated with baseline left ventricular mass, duration of therapy, the SBP reduction [505,506], and the drugs used, with ARBs, ACE inhibitors, and CCBs causing more effective LVH regression than beta-blockers [173] or diuretics.

In patients with HFrEF, antihypertensive drug treatment should start (if not already initiated) when BP is more than 140/90 mmHg. It is unclear how low BP should be lowered in patients with heart failure. Outcomes for patients with heart failure have repeatedly been shown to be poor if BP values are low, which suggests (although data interpretation is made difficult by the possibility of reversed causality) that it may be wise to avoid actively lowering BP to less than 120/70 mmHg. However, some patients may achieve even lower BP levels than this because of the desirability to remain on treatment with guideline-directed heart failure medications, which, if tolerated, should be continued because of their protective effect [136].

Continued

Heart failure guideline-directed medications are recommended for the treatment of hypertension in patients with HFrEF [136]. ACE inhibitors, ARBs, beta-blockers, and MRAs (e.g. spironolactone and eplerenone) are all effective in improving clinical outcome in patients with established HFrEF, whereas for diuretics, evidence is limited to symptomatic improvement. If further BP lowering is required, a dihydropyridine CCB may be considered. Sacubutril/valsartan lowers BP has also been shown to improve outcomes in patients with HFrEF, and is indicated for the treatment of HFrEF as an alternative to ACE inhibitors or ARBs [507]. Nondihydropyridine CCBs (diltiazem and verapamil), alpha-blockers, and centrally acting agents, such as moxonidine, should not be used.

Antihypertensive treatment is commonly needed in patients with HFpEF; the same BP threshold and target for drug treatment indicated for HFrEF should be used. The optimal treatment strategy for hypertensive patients with HFpEF is not known, but the strategy outlined above for HFrEF patients might also be the one to adopt in HFpEF patients. HFpEF patients commonly have multiple comorbidities that may adversely affect outcomes and complicate management.

| Therapeutic strategies in hypertensive patients with heart failure or LVH                                                                                                                   |                    |                    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Recommendations                                                                                                                                                                             | Class <sup>a</sup> | Level <sup>b</sup> |
| In hypertensive patients with heart failure (with reduced or preserved ejection fraction), BP-lowering treatment should be considered if BP is $\geq 140/90$ mmHg [136]. <sup>c</sup>       | <b>IIa</b>         | <b>B</b>           |
| In patients with HFrEF, it is recommended that BP-lowering treatment comprises an ACE inhibitor or ARB, and a beta-blocker and diuretic and/or MRA if required [136].                       | <b>I</b>           | <b>A</b>           |
| Dihydropyridine CCBs may be added if BP control is not achieved. <sup>d</sup>                                                                                                               | <b>IIb</b>         | <b>C</b>           |
| In patients with HFpEF, BP treatment threshold and target values should be the same as for HFrEF [136].                                                                                     | <b>IIa</b>         | <b>B</b>           |
| Because no specific drug has proven its superiority, all major agents can be used.                                                                                                          | <b>I</b>           | <b>C</b>           |
| In all patients with LVH:<br>■ It is recommended to treat with an RAS blocker in combination with a CCB or diuretic [504].<br>■ SBP should be lowered to a range of 120–130 mmHg [504,506]. | <b>I</b>           | <b>A</b>           |
|                                                                                                                                                                                             | <b>IIa</b>         | <b>B</b>           |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LVH, left ventricular hypertrophy; MRA, mineralocorticoid receptor antagonist; RAS, renin–angiotensin system; SBP, systolic blood pressure.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

<sup>c</sup> A lowest safety BP value is not given as many patients receiving intensive treatment for heart failure may achieve much lower BP levels than recommended BP targets.

<sup>d</sup> Non-dihydropyridines are not recommended in HFrEF but may be used in HFpEF.

## CEREBROVASCULAR DISEASE AND COGNITION

Hypertension is a major risk factor for haemorrhagic and ischaemic stroke, and a risk factor for recurrent stroke. BP management during the acute phase of haemorrhagic and ischaemic stroke remains an area of uncertainty. BP is often elevated at presentation with acute stroke, but often declines without intervention [508].

### ACUTE INTRACEREBRAL HAEMORRHAGE

In acute intracerebral haemorrhage, an increased BP is common and is associated with a greater risk of haematoma expansion, increased risk of death, and a worse prognosis for neurological recovery [509,510]. Results from an RCT suggested that immediate BP lowering (within 6 h) to less than 140/90 mmHg did not show benefit on the primary outcome of disability or death at 3 months, but might reduce haematoma expansion and improve functional recovery, and was generally safe [511]. A subsequent RCT, in which SBP was immediately reduced ( $<4.5$  h) from a mean of 200 mmHg to two different target intervals (140–170 vs. 110–139 mmHg), showed that more intensive BP lowering had no benefit on the same primary outcome and was associated with more renal adverse events [512]. Thus, we do not recommend treatment to immediately lower BP in patients with acute intracerebral haemorrhage. One possible caveat to this recommendation is patients with acute intracerebral haemorrhage and very severe hypertension (SBP  $\geq 220$  mmHg), for whom there are much fewer data. A meta-analysis [513] and secondary outcome data from one RCT [511] have suggested a possible benefit on functional recovery at 3 months, and that acute lowering of SBP to less than 180 mmHg in these patients might be beneficial. Thus, careful lowering of BP via i.v. infusion may be considered in patients with markedly elevated BP (SBP  $\geq 220$  mmHg).

### ACUTE ISCHAEMIC STROKE

The beneficial effects of BP reduction are even less clear in acute ischaemic stroke. A key consideration is whether the patient will receive thrombolysis, because observational studies have reported an increased risk of intracerebral haemorrhage in patients with a markedly elevated BP who received thrombolysis [514,515]. In patients receiving i.v. thrombolysis, BP should be lowered and maintained at less than 180/105 mmHg for at least the first 24 h after thrombolysis. The benefit of acute BP lowering in patients with acute ischaemic stroke who do not receive thrombolysis is uncertain. A meta-analysis suggested that BP lowering early after acute ischaemic stroke had a neutral effect on the prevention of death or dependency [516,517]. In such patients with markedly elevated SBP or DBP (i.e.  $\geq 220$  or  $\geq 120$  mmHg, respectively), clinical judgement should define whether to intervene with drug therapy, in which case a reasonable goal may be to lower BP by 15%, with close monitoring, during the first 24 h after stroke onset [516,518–520]. Patients with acute ischaemic stroke and a BP lower than this in the first 72 h after stroke do not seem to benefit from the introduction or reintroduction of BP-lowering medication [516,521]. For stable patients who remain hypertensive ( $\geq 140/90$  mmHg) more than 3 days after an acute ischaemic stroke, initiation or reintroduction of BP-lowering medication should be considered [522].

## PREVIOUS STROKE OR TRANSIENT ISCHAEMIC ATTACK

RCTs of antihypertensive treatment (placebo controlled) in patients with a previous stroke or TIA, in a stable clinical condition, and with BP more than 140/90 mmHg, have shown that BP lowering reduces the risk of recurrent stroke [338,523]. No evidence is yet available that recurrent stroke is prevented by initiating therapy when BP is in the high-normal range. We recommend resumption of BP-lowering therapy several days after stroke, or immediately after TIA, for previously treated or untreated patients

with hypertension, for prevention of both recurrent stroke and other cardiovascular events.

The appropriate BP targets to prevent recurrent stroke are uncertain, but should be considered in the context of a consistent finding in many meta-analyses that stroke is the one major cardiovascular event that is reduced at lower achieved BP levels. This is supported by the results from the recent Secondary Prevention of Small Subcortical Strokes 3 study [244,524] in patients with a recent lacunar stroke, which suggested an SBP target of less than 130 mmHg [525], and other studies [526].

| Therapeutic strategies in hypertensive patients with acute stroke and cerebrovascular disease                                                                                                               |                    |                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Recommendations                                                                                                                                                                                             | Class <sup>a</sup> | Level <sup>b</sup> |
| In patients with acute intracerebral haemorrhage:                                                                                                                                                           | III                | A                  |
| ■ Immediate BP lowering is not recommended for patients with SBP < 220 mmHg [509–513].                                                                                                                      |                    |                    |
| ■ In patients with SBP ≥ 220 mmHg, careful acute BP lowering with i.v. therapy to < 180 mmHg should be considered [509–513].                                                                                | IIa                | B                  |
| In acute ischaemic stroke, routine BP lowering with antihypertensive therapy is not recommended [516,517], with the exceptions:                                                                             | III                | A                  |
| ■ In patients with acute ischaemic stroke who are eligible for i.v. thrombolysis, BP should be carefully lowered and maintained at < 180/105 mmHg for at least the first 24 h after thrombolysis [514,515]. | IIa                | B                  |
| ■ In patients with markedly elevated BP who do not receive fibrinolysis, drug therapy may be considered, based on clinical judgement, to reduce BP by 15% during the first 24 h after the stroke onset.     | IIb                | C                  |
| In hypertensive patients with an acute cerebrovascular event, antihypertensive treatment is recommended:                                                                                                    | I                  | A                  |
| ■ Immediately for TIA [526].                                                                                                                                                                                |                    |                    |
| ■ After several days in ischaemic stroke [526].                                                                                                                                                             | I                  | A                  |
| In all hypertensive patients with ischaemic stroke or TIA, an SBP target range of 120–130 mmHg should be considered [244,524,526].                                                                          | IIa                | B                  |
| The recommended antihypertensive drug treatment strategy for stroke prevention is a RAS blocker plus a CCB or a thiazide-like diuretic [338].                                                               | I                  | A                  |

Abbreviations: BP, blood pressure; CCB, calcium channel blocker; i.v., intravenous; RAS, renin-angiotensin system; SBP, systolic blood pressure; TIA, transient ischaemic attack.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

Prevention of stroke is a consistent benefit of antihypertensive therapy and has been observed in all large RCTs using different drug regimens. However, individual RCTs comparing modern treatment regimens [317,527] and meta-analyses suggest that beta-blockers are less effective at stroke prevention than other classes of antihypertensive agents [2,528]. Although the beta-blocker in these studies was atenolol, there are no data with more modern beta-blockers with regards to stroke prevention in hypertension. Thus, optimal antihypertensive treatment for stroke prevention should not include beta-blockers unless there is a compelling indication for their use, mindful of the fact that the most common recurrent event after stroke is a further stroke rather than myocardial infarction [529].

## COGNITIVE DYSFUNCTION AND DEMENTIA

Several epidemiological and clinical studies have shown that hypertension in midlife predicts cognitive decline and dementia (both Alzheimer's disease and vascular dementia) in older patients [530–533]. However, evidence on the beneficial effects of BP lowering on cognitive decline is scant and conflicting. A meta-analysis [534] of 12 studies investigating the impact of different antihypertensive drugs on dementia and cognitive function concluded that

BP lowering reduced the incidence and risk of cognitive impairment and dementia by 9%. One study showed that achieving better BP control over 4 years reduced the progression of cerebral white matter lesions and the decrease in global cognitive performance [535].

Trials are urgently needed to better define the potential impact of BP lowering on preventing cognitive decline or in delaying dementia when cognitive dysfunction is already present.

## HYPERTENSION, ATRIAL FIBRILLATION, AND OTHER ARRHYTHMIAS

Hypertension predisposes to cardiac arrhythmias, including ventricular arrhythmias, but most commonly AF [536–538], which should be considered a manifestation of hypertensive heart disease [539]. Even high-normal BP is associated with incident AF [540,541], and hypertension is the most prevalent concomitant condition in AF patients. AF adds to the risk of stroke and heart failure. AF necessitates stroke prevention with oral anticoagulation, with monitoring of the associated risks and prevention of bleeding [542].



Most patients show a high ventricular rate with AF [542] and, in such patients, beta-blockers or non-dihydropyridine calcium antagonists (e.g. diltiazem and verapamil) are recommended as antihypertensive agents. Non-dihydropyridine CCBs should be avoided in patients with reduced left ventricular systolic function and may precipitate heart failure in some patients. Beta-blockers are often indicated in these patients, and may need to be combined with digoxin to gain rate control [542].

In RCTs of hypertensive patients with LVH and/or high cardiovascular risk [543,544], RAS blockers have been shown to reduce first occurrence of AF, compared with beta-blockers or CCBs, consistent with similar effects of RAS blockers in patients with heart failure [545–547]. RAS blockers do not prevent recurrence of paroxysmal or persistent AF [548–550]. In patients with heart failure, beta-blockers [551] and MRAs [552] may also prevent AF. The preventive effect of RAS blockers against the development of AF is indirectly supported by a general practice database in the UK, with approximately 5 million patient records, which has reported that ACE inhibitors, ARBs, and beta-blockers are associated with a lower risk of AF compared with CCBs [553]. Hence, RAS blockers should be considered as part of the antihypertensive treatment strategy in hypertensive patients with a high risk of AF (e.g. LVH), to prevent incident AF.

| Therapeutic strategies in hypertensive patients with AF                                                                                                                                                                                                                                                                                                                                                                                               |                    |                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Recommendation                                                                                                                                                                                                                                                                                                                                                                                                                                        | Class <sup>a</sup> | Level <sup>b</sup> |
| In patients with AF, screening for hypertension is recommended [536].                                                                                                                                                                                                                                                                                                                                                                                 | I                  | C                  |
| A beta-blocker or non-dihydropyridine CCB should be considered as part of the treatment of hypertension if rate control is needed [536].                                                                                                                                                                                                                                                                                                              | IIa                | B                  |
| Stroke prevention with oral anticoagulation is recommended in patients with AF and hypertension, and a CHA <sub>2</sub> DS <sub>2</sub> -VASc score of $\geq 2$ in men and $\geq 3$ in women [536, 556].                                                                                                                                                                                                                                              | I                  | A                  |
| Stroke prevention with oral anticoagulants should be considered in AF patients with hypertension, even when hypertension is the single additional risk factor (CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 1) [536, 556].                                                                                                                                                                                                                         | IIa                | B                  |
| Oral anticoagulants should be used with caution in patients with marked BP elevation (SBP $\geq 180$ mmHg and/or DBP $\geq 100$ mmHg); the aim should be to lower SBP to at least $<140$ mmHg, and SBP lowering to $<130$ should be considered. If this is not possible, then patients should make an informed decision that they accept that the stroke protection provided by the anticoagulant will be associated with higher bleeding risk [536]. | IIa                | B                  |

Abbreviations: AF, atrial fibrillation; BP, blood pressure; CCB, calcium channel blocker; CHA<sub>2</sub>DS<sub>2</sub>-VASc, Congestive heart failure, Hypertension, Age  $\geq 75$  years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female); DBP, diastolic blood pressure; SBP, systolic blood pressure.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

## ORAL ANTICOAGULANTS AND HYPERTENSION

Many patients requiring oral anticoagulants (e.g. with AF) will be hypertensive. Hypertension is not a contraindication to oral anticoagulant use. However, although its role has been unappreciated in most old and more recent RCTs on anticoagulant treatment [537], hypertension does substantially increase the risk of intracerebral haemorrhage when oral anticoagulants are used, and efforts should be directed towards achieving a BP goal of less than 130/80 mmHg in patients receiving oral anticoagulants. Detailed information on hypertension and oral anticoagulants has been published recently [526,536]. Anticoagulants should be used to reduce the risk of stroke in most AF patients with hypertension, including those with AF in whom hypertension is the single additional stroke risk factor [554,555]. BP control is important to minimize the risks of AF-related stroke and oral anticoagulant-related bleeding. Until more data are available, BP values in AF patients taking oral anticoagulants should be at least less than 140 mmHg for SBP and less than 90 mmHg for DBP. Oral anticoagulants should be used with caution in patients with persistent uncontrolled hypertension (SBP  $\geq 180$  mmHg and/or DBP  $\geq 100$  mmHg), and urgent efforts to control BP should be made.

## HYPERTENSION AND VASCULAR DISEASE

### CAROTID ATHEROSCLEROSIS

A small number of studies have reported the effects of the various pharmacological classes of antihypertensive drugs on carotid IMT, and very few on carotid plaques. Reducing BP regresses carotid IMT and may delay the intimal atherosclerotic process. There appear to be differential drug effects on IMT regression, with CCBs having greater efficacy than diuretics and beta-blockers [146], and ACE inhibitors more than diuretics [557]. However, the relevance of these findings is unclear because most patients receive combinations of treatment and the progression or treatment-induced changes in carotid IMT are poorly predictive of future cardiovascular events [184,558]. Patients with carotid plaques are at high risk of atheroembolic stroke and cardiovascular events, and BP lowering should be complemented by lifestyle advice and treatment with statins and antiplatelet therapy. A common conundrum faced by clinicians is the hypertensive patient with a tight carotid stenosis, especially when bilateral. No study has addressed this scenario and therefore advice is necessarily pragmatic, and we recommend a more cautious approach to BP lowering, initiating with monotherapy and carefully monitoring for adverse effects.

### ARTERIOSCLEROSIS AND INCREASED ARTERIAL STIFFNESS

Large artery stiffening is a major factor contributing to the rise in SBP and fall in DBP with ageing. Arterial stiffness is usually measured in studies as PWV. Arterial stiffening results from arteriosclerotic structural changes in large conduit arteries, leading to a loss of arterial elasticity, and the distending force resulting from the pressure exerted on the arterial wall. Thus, all antihypertensive drugs, by reducing BP, reduce arterial stiffness, as the reduction in BP unloads the stiff components of the arterial wall, leading to a passive decrease in PWV. Pharmacodynamic RCTs



[559] and meta-analyses [560,561] suggest that ACE inhibitors and ARBs may reduce PWV beyond the effect of BP lowering on a long-term basis. Whether RAS blockers are more effective than other antihypertensive drugs in this regard has not been demonstrated. Moreover, whether any long-term reduction in aortic stiffness [562] translates into a reduction in cardiovascular events beyond the impact of BP lowering alone [563] has not been demonstrated.

## LOWER EXTREMITY ARTERIAL DISEASE

LEAD is often a manifestation of more widespread atherosclerosis and especially atherosclerotic renal artery disease [564], and these patients are at very high cardiovascular risk [190]. BP control is an important part of the cardiovascular risk-reduction strategy in these patients. Beta-blockers have not been shown to worsen the symptoms of claudication in two meta-analyses [565,566]. Thus, beta-blockers remain a treatment option in hypertensive patients with LEAD when there is a specific indication for their use. When critical limb ischaemia is present, BP reduction should be instituted slowly as it may worsen ischaemia. In patients with LEAD, antihypertensive treatment should be complemented by lifestyle changes and especially smoking cessation, as well as statin and antiplatelet therapy [190].

| Therapeutic strategies in hypertensive patients with LEAD                                     |                    |                    |
|-----------------------------------------------------------------------------------------------|--------------------|--------------------|
| Recommendations                                                                               | Class <sup>a</sup> | Level <sup>b</sup> |
| BP-lowering treatment is recommended to reduce CV risk [2,190,503].                           | I                  | A                  |
| A combination of a RAS blocker, CCB, or diuretic should be considered as initial therapy [2]. | IIa                | B                  |
| Beta-blockers may also be considered [566].                                                   | IIb                | C                  |

Abbreviations: BP, blood pressure; CCB, calcium channel blocker; CV, cardiovascular; LEAD, lower extremity arterial disease; RAS, renin-angiotensin system.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

## HYPERTENSION IN VALVULAR DISEASE AND AORTOPATHY

### COARCTATION OF THE AORTA

When feasible, treatment of aortic coarctation is predominantly surgical and usually done in childhood. Even after surgical correction, these patients may develop systolic hypertension at a young age and require long-term follow-up. Few patients with aortic coarctation remain undetected until adult life, and by then often have severe hypertension, HMOD (especially LVH and left ventricular dysfunction), and an extensive collateral circulation below the coarctation. Such patients should be evaluated in a specialist centre. The medical therapy for hypertension in patients with aortic coarctation should follow the treatment algorithm outlined in section 'Treatment of hypertension', as there have been no formal RCTs to define optimal treatment strategies [567].

## PREVENTION OF AORTIC DILATION AND DISSECTION IN HIGH-RISK SUBJECTS

Chronic hypertension can be associated with modest aortic root dilatation. When more extensive aortic root dilatation is present or the dilatation extends beyond the aortic root, an additional cause for aortopathy should be sought. All hypertensive patients with aortic dilatation, whether associated with Marfan syndrome, bicuspid aortic valve disease, or not, should have their BP controlled  $\leq 130/80$  mmHg [568]. In patients with Marfan syndrome, prophylactic use of ACE inhibitors, ARBs, or beta-blockers seems to be able to reduce either the progression of the aortic dilatation or the occurrence of complications [568–570]. However, there is no evidence for the specific efficacy of these treatments in aortic disease of other aetiologies.

## HYPERTENSION BICUSPID AORTIC VALVE-RELATED AORTOPATHY

Bicuspid aortic valve disease occurs in 1 in 100 people, more often men, and is associated with coexistent aortic coarctation, which should be excluded in patients with bicuspid aortic valve disease. Bicuspid aortic valve disease is associated with an aortopathy, and the risk of development of aortic dilatation is higher in patients with bicuspid aortic valve disease than in the normal population [571] and is probably exacerbated by hypertension. Beyond aortic dilatation and aneurysm formation, bicuspid aortic valve disease is also a risk factor for dissection and rupture [572]. Thus, BP should be tightly controlled in patients with bicuspid aortic valve disease and targeted  $\leq 130/80$  mmHg if tolerated. There is popular misconception that BP-lowering treatment has deleterious effects in patients with aortic stenosis and hypertension, when in fact it is well tolerated even in patients with severe aortic stenosis. Moreover, vasodilating drugs (including RAS blockers) also appear to be well tolerated. Thus, treatment of hypertension should be considered in these patients [573].

## HYPERTENSION AND SEXUAL DYSFUNCTION

Sexual dysfunction may have an important negative effect on the quality of life of both men and women. Compared with the normotensive population, the prevalence of sexual dysfunction is greater in hypertensive individuals, in whom it presents an important cause of low adherence to or discontinuation of antihypertensive treatment [574]. A large meta-analysis of prospective cohort studies has provided strong evidence that in men, erectile dysfunction (i.e. inadequate penile erection) is a significant independent risk factor for cardiovascular events and mortality [575], which means that it may be viewed as an early marker of vascular damage [576]. Sexual dysfunction may be triggered or aggravated by treatment with thiazide or thiazide-like diuretics, conventional beta-blockers, or centrally acting agents (e.g. clonidine), while ACE inhibitors, ARBs, CCBs, or vasodilating beta-blockers may have neutral or even beneficial effects [574,577]. Phosphodiesterase-5 inhibitors are effective against erectile dysfunction in patients with hypertension. They should be given only in the absence of nitrate administration, but prescription also appears to be safe in patients with multidrug BP-lowering treatment [578], with some caution if treatment includes alpha-blockers [577]. However, it seems prudent for

unstable patients with high cardiovascular risk or severe uncontrolled hypertension to defer sexual activity until their condition is stabilized and treatment for erectile dysfunction can be initiated [575]. Overall, studies on the effects of hypertension and antihypertensive therapy on female sexual dysfunction are limited, and the situation is thus less clear than in men [577,579], although in a recent cross-sectional analysis among middle-aged and older treated hypertensive women in the SPRINT trial, neither BP values nor antihypertensive medication was associated with sexual dysfunction [579].

It is recommended that information on sexual dysfunction is collected in all hypertensive patients at diagnosis and regularly at the follow-up visits, with special attention to its possible relationship with reluctance to start or adherence to drug treatment. In men reporting sexual dysfunction, the antihypertensive agents more likely to be associated with this effect (e.g. beta-blockers and thiazide diuretics) should be avoided or replaced, unless strictly necessary for the patient's clinical condition.

## HYPERTENSION AND CANCER THERAPY

Hypertension is the most common cardiovascular comorbidity reported in cancer registries, in which an elevated BP is usually found in more than one-third of the patients [580]. This can be due to the high prevalence of hypertension at an age in which cancer is also common. However, it is also due to the pressor effect of two groups of widely used anticancer drugs, the inhibitors of the vascular endothelial growth factor signalling pathway (bevacizumab, sorafenib, sunitinib, and pazopanib) and the proteasome inhibitors (carfilzomib). While the former group of drugs inhibits the production of nitric oxide in the arterial wall, the latter reduces the vasodilator response to acetylcholine, favouring vasoconstriction and vasospasm [581].

In patients under treatment with the above-mentioned anticancer drugs, a BP increase has been reported in a variable but overall high percent of patients ( $\leq 30\%$ ). The increase frequently occurs during the first months after starting the anticancer therapy, the temporal association providing evidence for the anticancer drug's pathophysiological role. It follows that office BP should be measured weekly during the initial part of the first cycle of therapy and at least every 2–3 weeks thereafter [582]. After the first cycle is completed and BP values appear to be stable, BP can be measured at the time of the routine clinical evaluations or assessed by HBPM. Patients developing hypertension ( $\geq 140/90$  mmHg), or showing an increase in DBP  $\geq 20$  mmHg compared with pretreatment values, should initiate or optimize antihypertensive therapy, for which RAS blockers and CCBs may be considered the preferred drugs, and a RAS blocker-CCB combination is a frequently needed strategy. CCBs should only be of the dihydropyridine type, because diltiazem and verapamil block the CYP3A4 isoenzyme, which is involved in the metabolic pathway of sorafenib, increasing the drug's levels and leading to potential toxicity [583]. Although anticancer therapy takes an obvious priority, its temporary discontinuation may be considered when BP values are exceedingly high despite multidrug treatment, in the presence of severe hypertension-generated symptoms, or when there is a cardiovascular event requiring an immediate effective BP control [584].

## PERIOPERATIVE MANAGEMENT OF HYPERTENSION

With the increasing number of patients undergoing surgery, management of hypertension in the perioperative period (a term that includes the intraoperative phase) has emerged as an important issue in clinical practice [585]. ESC Guidelines have been issued for the assessment of cardiovascular variables, risk, and disease management of patients undergoing noncardiac surgery [586]. While a BP elevation is per se not a strong risk factor for cardiovascular complications in noncardiac surgery, overall cardiovascular risk assessment, including the search for HMOD, is important in treated and untreated hypertensive patients, and mandatory when a BP elevation is newly detected [537,586]. Postponing necessary surgery is usually not warranted in patients with grade 1 or 2 hypertension, whereas in those with an SBP at least 180 mmHg and/or DBP at least 110 mmHg, deferring the intervention until BP is reduced or controlled is advisable, except for emergency situations. What seems to be also important is to avoid large perioperative BP fluctuations [537,586]. This approach is supported by the findings from a recent RCT that has shown that in patients undergoing abdominal surgery, an individualized intraoperative treatment strategy, which kept BP values within a 10% difference from the preoperative office SBP, resulted in reduced risk of postoperative organ dysfunction [587]. There is no clear evidence in favour or against one vs. another antihypertensive treatment mode in patients undergoing noncardiac surgery, and thus the general drug treatment algorithms apply to these patients as well [588,589]. However, the perioperative use of betablockers has been the object of controversy for many years, and the concern has recently been revived by meta-analyses showing some increase in the risk of hypotension, stroke, and mortality in patients on perioperative beta-blockers vs. placebo [586,588,589]. Continuation of beta-blockers is nevertheless recommended in hypertensive patients on chronic beta-blocker treatment [586] in whom their abrupt discontinuation may lead to BP or heart rate rebounds [537]. This may also occur with the abrupt discontinuation of central agents such as clonidine. More recently, the question has been raised whether RAS blockers should be discontinued before surgery to reduce the risk of intraoperative hypotension [586,590]. Preoperative discontinuation of these drugs has also been supported by a recent international prospective cohort study, in a heterogeneous group of patients, in which withholding ACE inhibitors or ARBs 24 h before noncardiac surgery was associated with a significant reduction in cardiovascular events and mortality 30 days after the intervention [591].

### Perioperative management of hypertension

| Recommendations                                                                                                                                                         | Class <sup>a</sup> | Level <sup>b</sup> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| It is recommended that newly diagnosed hypertensive patients who are scheduled for elective surgery should be preoperatively screened for HMOD and cardiovascular risk. | I                  | C                  |
| It is recommended to avoid large perioperative BP fluctuations during the perioperative period [587].                                                                   | I                  | C                  |

Continued

|                                                                                                                                              |            |          |
|----------------------------------------------------------------------------------------------------------------------------------------------|------------|----------|
| Non-cardiac surgery may not be deferred in patients with grade 1 or 2 hypertension (SBP < 180 mmHg; DBP < 110 mmHg).                         | <b>IIb</b> | <b>C</b> |
| Perioperative continuation of beta-blockers is recommended in hypertensive patients on chronic treatment with these drugs [592,593].         | <b>I</b>   | <b>B</b> |
| Abrupt discontinuation of beta-blockers or centrally acting agents (e.g. clonidine) is potentially harmful and is not recommended [589,594]. | <b>III</b> | <b>B</b> |
| Transient preoperative discontinuation of RAS blockers should be considered in patients with hypertension undergoing non-cardiac surgery.    | <b>IIa</b> | <b>C</b> |

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; HMOD, hypertension-mediated organ damage; RAS, renin-angiotensin system; SBP, systolic blood pressure.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

## MANAGING CONCOMITANT CARDIOVASCULAR DISEASE RISK

### STATINS AND LIPID-LOWERING DRUGS

Patients with hypertension, and more so those with type 2 diabetes or metabolic syndrome, often have atherogenic dyslipidaemia characterized by elevated triglycerides and LDL cholesterol (LDL-C), and low HDL cholesterol (HDL-C) [595]. The benefit of adding a statin to antihypertensive treatment was well established in the ASCOT-Lipid Lowering Arm study [596] and further studies, as summarized in previous European Guidelines [16,35]. The beneficial effect of statin administration to patients without previous cardiovascular events [targeting an LDL-C value of less than 3.0 mmol/L (115 mg/dL)] has been strengthened by the findings from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) [597] and HOPE-3 studies [343,598], showing that lowering LDL-C in patients with baseline values less than 3.4 mmol/L (130 mg/dL) reduced the incidence of cardiovascular events by between 44 and 24%. This justifies the use of statins in hypertensive patients who have moderate–high cardiovascular risk [599].

As detailed in the recent ESC/EAS Guidelines [599], when overt CVD is present and the cardiovascular risk is very high, statins should be administered to achieve LDL-C levels of less than 1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) [600–602]. In patients at high cardiovascular risk, an LDL-C goal of less than 2.6 mmol/L (100 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended [602]. Beneficial effects of statin therapy have also been shown in patients with a previous stroke with LDL-C targets less than 2.6 mmol/L (100 mg/dL) [525]. Whether they also benefit from a target of less than 1.8 mmol/L (70 mg/dL) is open to future research. The summary of the available evidence suggests that many patients with hypertension would benefit from statin therapy.

## ANTIPLATELET THERAPY AND ANTICOAGULANT THERAPY

The most common complications of hypertension are related to thrombosis [603]. Hypertension predisposes to a prothrombotic state [603], and also predisposes to LEAD, heart failure, or AF, which are common conditions associated with thromboembolism, whether systemic or venous. Antiplatelet and anticoagulant therapy use in patients with hypertension was addressed in a Cochrane systematic review [604], which included four randomized trials with a combined total of 44–012 patients. The authors concluded that overall acetylsalicylic acid (aspirin) did not reduce stroke or cardiovascular events compared with placebo in primary prevention patients with elevated BP and no previous CVD [604]. For secondary prevention, antiplatelet therapy in patients with elevated BP was reported as causing an absolute reduction in vascular events of 4.1% compared with placebo [604].

Benefit has not been demonstrated for anticoagulation therapy, alone or in combination with aspirin, in patients with hypertension in the absence of other indications requiring anticoagulants, such as AF or venous thromboembolism [604]. In anticoagulated patients, uncontrolled hypertension is one of the independent risk factors for intracranial haemorrhage and major bleeding [605]. In such patients, attention to modifiable bleeding risk factors should be made during all patient contacts. Bleeding risk assessment with clinical risk scores such as the HAS-BLED [Hypertension, Abnormal renal/liver function (1 point each), Stroke, Bleeding history or predisposition, Labile INR, Older (>65), Drugs/alcohol concomitantly (1 point each)] score, includes uncontrolled hypertension (defined as SBP >160 mmHg) as one of the risk factors for bleeding [606]; these should be used to 'flag up' patients at particularly high risk (e.g. HAS-BLED 3) for more regular review and follow-up [607].

### Treatment of CV risk factors associated with hypertension

| Recommendations                                                                                                                                                                                                         | Class <sup>a</sup> | Level <sup>b</sup> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Cardiovascular risk assessment with the SCORE system is recommended for hypertensive patients who are not already at high or very high risk due to established CVD, renal disease, or diabetes [33].                    | <b>I</b>           | <b>B</b>           |
| For patients at very high cardiovascular risk, statins are recommended to achieve LDL-C levels of <1.8 mmol/L (70 mg/dL), or a reduction of ≥ 50% if the baseline LDL-C is 1.8–3.5 mmol/L (70–135 mg/dL) [596,599,602]. | <b>I</b>           | <b>B</b>           |
| For patients at high cardiovascular risk, statins are recommended to achieve an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of ≥ 50% if the baseline LDL-C is 2.6–5.2 mmol/L (100–200 mg/dL) [599,602].       | <b>I</b>           | <b>B</b>           |
| For patients at low–moderate cardiovascular risk, statins should be considered to achieve an LDL-C value of <3.0 mmol/L (115 mg/dL) [598].                                                                              | <b>IIa</b>         | <b>C</b>           |

Continued



|                                                                                                                                  |     |   |
|----------------------------------------------------------------------------------------------------------------------------------|-----|---|
| Antiplatelet therapy, in particular low-dose aspirin, is recommended for secondary prevention in hypertensive patients [35,604]. | I   | A |
| Aspirin is not recommended for primary prevention in hypertensive patients without CVD [35,604].                                 | III | A |

Abbreviations: CVD, cardiovascular disease; LDL-C, LDL cholesterol; SCORE, Systematic COronary Risk Evaluation.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

In summary, aspirin is not recommended for primary prevention in hypertensive patients without CVD [35]. For secondary prevention, the benefit of antiplatelet therapy in patients with hypertension may be greater than the harm [35,604]. Ticlopidine, clopidogrel, and newer antiplatelet agents such as prasugrel and ticagrelor have not been sufficiently evaluated in patients with high BP.

## GLUCOSE-LOWERING DRUGS AND BLOOD PRESSURE

The impact of new glucose-lowering drugs on BP and the reduction in cardiovascular and renal risk, beyond their effect of glucose control, have received attention after the publication of the US Food and Drug Administration recommendations for evaluating cardiovascular risk in new therapies to treat type 2 diabetes. New generations of antidiabetes drugs, that is dipeptidyl peptidase 4 inhibitors and glucagon-like peptide 1 agonists, slightly reduce BP, and also body weight with glucagon-like peptide 1 agonists. Two glucagon-like peptide 1 agonists (liraglutide and semaglutide) reduced cardiovascular and total mortality, but not heart failure, in patients with type 2 diabetes [608,609]. More data are required with respect to the capacity of glucagon-like peptide 1 agonists and dipeptidyl peptidase 4 inhibitors to prevent heart failure.

Inhibitors of sodium-glucose co-transporter-2 are the only glucose-lowering drug class to reduce BP beyond the projected impact of weight reduction on BP. Empagliflozin [475] and canagliflozin [476] have demonstrated a reduction in heart failure and total and cardiovascular mortality, and a protective effect on renal function. Several mechanisms may account for these effects, and increased sodium excretion and improvements in tubuloglomerular balance reducing hyperfiltration are suggested mechanisms for the observed cardiovascular and renal protection, respectively.

## PATIENT FOLLOW-UP

### FOLLOW-UP OF HYPERTENSIVE PATIENTS

After the initiation of antihypertensive drug therapy, it is important to revisit the patient at least once within the first 2 months to evaluate the effects on BP and assess possible side effects until BP is under control. The frequency of revisiting will depend on the severity of hypertension, the urgency to achieve BP control, and the patient's comorbidities. SPC therapy should reduce BP within 1–2 weeks

and may continue to reduce BP over the next 2 months. Once the BP target is reached, a visit interval of a few months is reasonable and evidence has been obtained that no difference exists in BP control between 3-month and 6-month intervals [610]. Depending on the local organization of health resources, many of the later visits may be performed by nonphysician health workers such as nurses [611]. For stable patients, HBPM and electronic communication with the physician may also provide an acceptable alternative to reduce the frequency of visits [60,612,613]. It is nevertheless advisable to assess risk factors and asymptomatic organ damage at least every 2 years.

## FOLLOW-UP OF SUBJECTS WITH HIGH-NORMAL BLOOD PRESSURE AND WHITE-COAT HYPERTENSION

Patients with high-normal BP or white-coat hypertension frequently have additional risk factors, including HMOD, and have a higher risk of developing sustained hypertension [427,614–618] (see section 'Blood pressure measurement'). Thus, even when untreated, they should be scheduled for regular follow-up (at least annual visits) to measure office and out-of-office BP, as well as to check the cardiovascular risk profile. At annual visits, recommendations on lifestyle changes, which represent the appropriate treatment in many of these patients, should be reinforced.

## ELEVATED BLOOD PRESSURE AT CONTROL VISITS

The finding of an elevated BP should always lead physicians to search for the cause(s), particularly the most common ones such as poor adherence to the prescribed treatment regimen, persistence of a white-coat effect, and occasional or more regular consumption of salt, drugs, or substances that raise BP or oppose the antihypertensive effect of treatment (e.g. alcohol or nonsteroidal anti-inflammatory drugs). This may require tactful but stringent questioning of the patient (and his/her relatives) to identify interfering factors, as well as repeated measurements of BP in the following weeks to ensure that BP has returned to controlled values. If ineffective treatment is regarded as the reason for inadequate BP control, the treatment regimen should be uptitrated in a timely fashion (see section 'Treatment of hypertension'); this avoids clinical inertia, a major contributor to poor BP control worldwide [311].

## IMPROVEMENT IN BLOOD PRESSURE CONTROL IN HYPERTENSION: DRUG ADHERENCE

There is growing evidence that poor adherence to treatment – in addition to physician inertia (i.e. lack of therapeutic action when the patient's BP is uncontrolled) – is the most important cause of poor BP control [293,619–621]. Nonadherence to antihypertensive therapy correlates with higher risk of cardiovascular events [312,622].

Early discontinuation of treatment and suboptimal daily use of the prescribed regimens are the most common facets of poor adherence. After 6 months, more than one-third, and after 1 year, about one-half of patients may stop their initial treatment [623]. Studies based on the detection

of antihypertensive medications in blood or urine have shown that low adherence to the prescribed medications can affect or less 50% of patients with apparently resistant hypertension [352,624], and that poor adherence is strongly and inversely correlated with the number of pills prescribed. Early recognition of a lack of adherence might reduce the number of costly investigations and procedures (including interventional treatment), and avoid the prescription of unnecessary drugs [625].

A major emphasis of these Guidelines has been to simplify the treatment strategy to try and improve adherence to treatment and BP control, by prescribing a single pill to most patients with hypertension. This is a response to the fact that despite the clear-cut benefits of BP treatment in trials, most treated patients do not achieve recommended BP targets in real life. The lower BP targets recommended in these Guidelines will mean that BP control rates will be even worse unless action is taken to ensure that patients are more likely to adhere to logical combinations of treatment. Several methods are available to detect poor adherence, but most are indirect, poorly reliable, and provide little information on the most important issue: dosing history. Today, the most accurate methods that can be recommended, despite their limitations, are the detection of prescribed drugs in blood or urine samples. Directly observed treatment, followed by BP measurement over subsequent hours via HBPM or ABPM, can also be very useful to determine if BP really is poorly controlled despite witnessed consumption of medication in patients with apparent resistant hypertension. In contrast, questionnaires frequently overestimate drug adherence. The assessment of adherence should be improved with the development of cheaper and more reliable methods of detection that are easily applicable in daily practice [354,626].

Barriers to optimal adherence may be linked with physician attitudes, patient beliefs and behaviour, the complexity and tolerability of drug therapies, the healthcare system, and several other factors. Therefore, the assessment of adherence should always be conducted in a no-blame approach, and should favour an open discussion to identify the specific barriers limiting the patient's ability to follow the therapeutic recommendations. Individualized solutions should be found. Patients should be encouraged to take responsibility for their own cardiovascular health.

Patient adherence to therapy can be improved by several interventions. The most useful interventions are those linking drug intake with habits [347], those giving adherence feedback to patients, self-monitoring of BP [64] using pill boxes and other special packaging, and motivational interviewing. Increasing the integration among healthcare providers with the involvement of pharmacists and nurses increases drug adherence. Using multiple components has a greater effect on adherence, as the effect size of each intervention is generally modest. Recent data suggest that adherence to treatment may also be improved with the use of telemetry for transmission of recorded home values, maintaining contact between patients and physicians, and studies are ongoing [627].

Prescription of an appropriate therapeutic regimen is crucial [389]. This might be achieved through: possible drug-related adverse events, using long-acting drugs that require once daily dosage [628,629], avoiding complex dosing schedules, using SPCs whenever possible, and taking into consideration the effect of treatment on a patient's budget.

Compared with the large number of trials for individual drugs and treatments, there are only a limited number

**Table 65.33** Interventions that may improve drug adherence in hypertension

#### Physician level

- Provide information on the risks of hypertension and the benefits of treatment, as well as agreeing a treatment strategy to achieve and maintain BP control using lifestyle measures and a single-pill-based treatment strategy when possible (information material, programmed learning, and computer-aided counselling)
- Empowerment of the patient
- Feedback on behavioural and clinical improvements
- Assessment and resolution of individual barriers to adherence
- Collaboration with other healthcare providers, especially nurses and pharmacists

#### Patient level

- Self-monitoring of BP (including telemonitoring)
- Group sessions
- Instruction combined with motivational strategies
- Self-management with simple patient-guided systems
- Use of reminders
- Obtain family, social, or nurse support
- Provision of drugs at worksite

#### Drug treatment level

- Simplification of the drug regimen favouring the use of SPC therapy
- Reminder packaging

#### Health system level

- Supporting the development of monitoring systems (telephone follow-up, home visits, and telemonitoring of home BP)
- Financially supporting the collaboration between healthcare providers (e.g. pharmacists and nurses)
- Reimbursement of SPC pills
- Development of national databases, including prescription data, available for physicians and pharmacists
- Accessibility to drugs

Abbreviations: BP, blood pressure; SPC, single-pill combination.

of rigorous trials on adherence interventions. Thus, the level of evidence indicating that a sustained improvement in medication adherence can be achieved within the resources available today in clinical practice is low. This is essentially due to the short duration of most studies, their heterogeneity, and their questionable designs. Whether available interventions ameliorate treatment outcomes remains to be demonstrated in adequate trials.

A list of the interventions associated with improved patient adherence to treatment is shown in Table 65.33.

## CONTINUED SEARCH FOR ASYMPTOMATIC HYPERTENSION-MEDIATED ORGAN DAMAGE

The importance and need to detect HMOD at initial assessment to help risk stratify the patient, and to review the progression or regression of HMOD during follow-up, have been described in section 'Blood pressure measurement'. The presence of HMOD demonstrates that BP is elevated and that the patient would benefit from treatment. The regression of asymptomatic organ damage occurring during treatment can often indicate an improved prognosis (see section 'Clinical evaluation and assessment of hypertension-mediated organ damage in patients with hypertension').



## CAN ANTIHYPERTENSIVE MEDICATIONS BE REDUCED OR STOPPED?

In some patients in whom treatment is accompanied by effective BP control for an extended period, it may be possible to reduce the number and/or dosage of drugs. This may particularly be the case if BP control is accompanied by healthy lifestyle changes such as weight loss, exercise habit, and a low-fat and low-salt diet, which remove environmental pressor influences. A reduction of medications should be made gradually, and the patient should be checked frequently because reappearance of hypertension can occur quickly, within weeks, or may take many months. Patients with prior HMOD or previous accelerated hypertension should not have their treatment withdrawn.

### GAPS IN THE EVIDENCE

#### Gaps in the evidence and need for further studies

|                                                                                                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| What is the optimal population screening programme for detecting hypertension?                                                                                                         |
| What is the optimal method to measure BP in patients with AF?                                                                                                                          |
| What is the incremental benefit for cardiovascular risk prediction of the addition of out-of-office BP (HBPM and ABPM) to office BP measurement?                                       |
| What is the incremental benefit, over the SCORE system, of measures of HMOD in reclassifying the cardiovascular risk of patients with hypertension?                                    |
| What are the appropriate BP thresholds and targets for drug treatment in younger hypertensive patients?                                                                                |
| What are the optimal BP treatment targets according to HBPM and ABPM?                                                                                                                  |
| What are the outcome benefits associated with antihypertensive treatment in patients with resistant hypertension?                                                                      |
| What are the benefits of BP treatment for patients with BP in the high-normal range?                                                                                                   |
| What baseline level of cardiovascular risk predicts treatment benefit?                                                                                                                 |
| More data on the benefits of BP treatment in the very elderly and the influence of frailty                                                                                             |
| Outcome-based comparison between office BP and out-of-office BP-guided treatment                                                                                                       |
| Outcome-based comparison between treatments guided by BP control and by HMOD reductions, especially in younger patients                                                                |
| More outcome studies of the optimal SBP treatment target for patients at different levels of baseline cardiovascular risk and with different comorbidities, including diabetes and CKD |
| More outcome studies of the optimal DBP treatment target                                                                                                                               |
| Impact of single-pill vs. multidrug treatment strategies on adherence to treatment, BP control, and clinical outcomes                                                                  |
| Outcome-based comparison between treatment strategies based on initial monotherapy vs. initial combination therapy                                                                     |

Continued

|                                                                                                    |
|----------------------------------------------------------------------------------------------------|
| What is the optimal salt intake to reduce cardiovascular and mortality risk?                       |
| What are the long-term outcome benefits resulting from the recommended lifestyle changes?          |
| Outcome-based comparison between treatments based on thiazide vs. thiazide-like diuretics          |
| Incremental value of central vs. peripheral BP in risk estimation and risk reduction by treatment  |
| Outcome-based comparison of BP treatment with classical vs. vasodilator beta-blockers              |
| Optimal BP treatment targets in specific clinical conditions (e.g. diabetes, CKD, and post-stroke) |
| Protective effect of antihypertensive treatment in patients with cognitive dysfunction or dementia |
| Role of antihypertensive treatment in white-coat hypertension                                      |
| Role of antihypertensive treatment in masked hypertension                                          |
| Optimal treatment of hypertension in different ethnic groups                                       |

Abbreviations: ABPM, ambulatory blood pressure monitoring; AF, atrial fibrillation; BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; HBPM, home blood pressure monitoring; HMOD, hypertension-mediated organ damage; SBP, systolic blood pressure; SCORE, Systematic COronary Risk Evaluation.

### KEY MESSAGES

1. *BP, epidemiology, and risk.* Globally, over 1 billion people have hypertension. As populations age and adopt more sedentary lifestyles, the worldwide prevalence of hypertension will continue to rise towards 1.5 billion by 2025. Elevated BP is the leading global contributor to premature death, accounting for almost 10 million deaths in 2015, 4.9 million due to ischaemic heart disease and 3.5 million due to stroke. Hypertension is also a major risk factor for heart failure, AF, CKD, PAD, and cognitive decline.
2. *Definition of hypertension.* The classification of BP and the definition of hypertension is unchanged from previous European Guidelines, and is defined as an office SBP at least 140 and/or DBP at least 90 mmHg, which is equivalent to a 24 h ABPM average of at least 130/80 mmHg, or a HBPM average at least 135/85 mmHg.
3. *Screening and diagnosis of hypertension.* Hypertension is usually asymptomatic (hence the term 'silent killer'). Because of its high prevalence, screening programmes should be established to ensure that BP is measured in all adults at least every 5 years, and more frequently in people with a high-normal BP. When hypertension is suspected because of an elevated screening BP, the diagnosis of hypertension should be confirmed either by repeated office BP measurements over a number of visits or by out-of-office BP measurement using 24 h ABPM or HBPM.
4. *The importance of cardiovascular risk assessment and detection of HMOD.* Other cardiovascular risk factors such as dyslipidaemia and metabolic syndrome frequently cluster with hypertension. Thus, unless the patient

is already at high or very high risk due to established CVD, formal cardiovascular risk assessment is recommended using the SCORE system. However, it is important to recognize that the presence of HMOD, especially LVH, CKD, or advanced retinopathy, further increases the risk of cardiovascular morbidity and mortality, and should be screened for as part of risk assessment in hypertensive patients because the SCORE system alone may underestimate their risk.

5. *Think: could this patient have secondary hypertension?* For most people with hypertension, no underlying cause will be detected. Secondary (and potentially remediable) causes of hypertension are more likely to be present in people with young onset of hypertension (<40 years), people with severe or treatment-resistant hypertension, or people who suddenly develop significant hypertension in midlife on a background of previously normal BP. Such patients should be referred for specialist evaluation.
6. *Treatment of hypertension: importance of lifestyle interventions.* The treatment of hypertension involves lifestyle interventions and drug therapy. Many patients with hypertension will require drug therapy, but lifestyle interventions are important because they can delay the need for drug treatment or complement the BP-lowering effect of drug treatment. Moreover, lifestyle interventions such as sodium restriction, alcohol moderation, healthy eating, regular exercise, weight control, and smoking cessation all have health benefits beyond their impact on BP.
7. *When to consider drug treatment of hypertension.* The treatment thresholds for hypertension are now less conservative than they were in previous Guidelines. We now recommend that patients with low-moderate-risk grade 1 hypertension (office BP 140–159/90–99), even if they do not have HMOD, should now receive drug treatment if their BP is not controlled after a period of lifestyle intervention alone. For higher-risk patients with grade 1 hypertension, including those with HMOD, or patients with higher grades of hypertension (e.g. grade 2 hypertension,  $\geq 160/100$  mmHg), we recommend initiating drug treatment alongside lifestyle interventions. These recommendations apply to all adults aged <80 years.
8. *Special considerations in frail and older patients.* It is increasingly recognized that biological rather than chronological age, as well as consideration of frailty and independence, are important determinants of the tolerability of and likely benefit from BP-lowering medications. It is important to note that even in the very old (i.e. >80 years), BP-lowering therapy reduces mortality, stroke, and heart failure. Thus, these patients should not be denied treatment or have treatment withdrawn simply on the basis of age. For people more than 80 years who have not yet received treatment for their BP, treatment is recommended when their office SBP is at least 160 mmHg, provided that the treatment is well tolerated.
9. *How low should SBP be lowered?* This has been a hotly debated topic. A key discussion point is the balance of potential benefits vs. potential harm or adverse effects. This is especially important whenever BP targets are lowered, as there is a greater potential for harm to exceed benefit. Thus, in these Guidelines, we recommend a target range. The evidence strongly suggests that lowering office SBP to <140 mmHg is beneficial for all patient groups, including independent older patients. There is also evidence to support targeting SBP to 130 mmHg for most patients, if tolerated. Even lower SBP levels (<130 mmHg) will be tolerated and potentially beneficial for some patients, especially to further reduce the risk of stroke. SBP should not be targeted to less than 120 mmHg because the balance of benefit vs. harm becomes concerning at these levels of treated SBP.
10. *BP targets in old and very old patients.* As discussed above, independence, frailty, and comorbidities will all influence treatment decisions, especially in older ( $\geq 65$  years) and very old (>80 years) patients. The desired SBP target range for all patients aged more than 65 years is 130–139 mmHg. This is lower than in previous Guidelines and may not be achievable in all older patients, but any BP lowering towards this target is likely to be beneficial provided that the treatment is well tolerated.
11. *BP targets in patients with diabetes and/or CKD.* The BP treatment targets for patients with diabetes or kidney disease have been a moving target in previous Guidelines because of seemingly contradictory results from major outcome trials and meta-analyses. For diabetes, targeting the SBP to less than 140 mmHg and towards 130 mmHg, as recommended for all other patient groups, is beneficial on major outcomes. Moreover, targeting SBP to less than 130 mmHg, for those who will tolerate it, may further reduce the risk of stroke but not other major outcomes. SBP should not be less than 120 mmHg. For patients with CKD, the evidence suggests that the target BP range should be 130–139 mmHg.
12. *How low should DBP be lowered?* The optimal DBP target has been less well defined, but a DBP target of less than 80 mmHg is recommended. Some patients with stiff arteries and isolated systolic hypertension will already have DBP levels below this target. These are high-risk patients and the low DBP should not discourage treatment of their elevated SBP to the recommended target, provided that treatment is well tolerated.
13. *The need to do better on BP control.* A key message in these Guidelines is the need to do better at improving BP control rates. Despite the overwhelming evidence of treatment benefit, on average, less than 50% of patients with treated hypertension achieve an SBP target of less than 140 mmHg. Physician inertia (inadequate uptitration of treatment, especially from monotherapy) and poor patient adherence to treatment (especially when based on multiple pills) are now recognized as the major factors contributing to poor BP control.
14. *Start treatment in most patients with two drugs, not one.* Monotherapy is usually inadequate therapy for most people with hypertension; this will be especially true now that the BP treatment targets for many patients are lower than in previous Guidelines. These Guidelines have set out to normalize the concept that initial therapy for the majority of patients with hypertension should be with a combination of two drugs, not a single drug. The only exception would be in a limited number of patients with a lower baseline BP close to their recommended target, who might achieve that target with a single drug, or in some frailer old or very old patients in whom more gentle

reduction of BP may be desirable. Evidence suggests that this approach will improve the speed, efficiency, and consistency of initial BP lowering and BP control, and is well tolerated by patients.

15. *A single-pill strategy to treat hypertension.* Poor adherence to longer-term BP-lowering medication is now recognized as a major factor contributing to poor BP control rates. Research has shown a direct correlation between the number of BP-lowering pills and poor adherence to medications. Moreover, SPC therapy has been shown to improve adherence to treatment. SPC therapy is now the preferred strategy for initial two-drug combination treatment of hypertension and for three-drug combination therapy when required. This will control the BP of most patients with a single pill and could transform BP control rates.
16. *A simplified drug treatment algorithm.* We have simplified the treatment strategy so that patients with uncomplicated hypertension and many patients with a variety of comorbidities (e.g. HMOD, diabetes, PAD, or cerebrovascular disease) receive similar medication. We recommend a combination of an ACE inhibitor or ARB with a CCB or thiazide/ thiazide-like diuretic as initial therapy for most patients. For those requiring three drugs, we recommend a combination of an ACE inhibitor or ARB with a CCB and a thiazide/thiazide-like diuretic. We recommend that beta-blockers be used when there is a specific indication for their use (e.g. angina, postmyocardial infarction, HFrEF, or when heart rate control is required).
17. *Hypertension in women and in pregnancy.* In women with hypertension who are planning pregnancy, ACE inhibitors or ARBs and diuretics should be avoided, and the preferred medications to lower BP, if required, include alpha-methyl dopa, labetalol, or CCBs. The same drugs are suitable if BP lowering is required in pregnant women. ACE inhibitors or ARBs should not be used in pregnant women.
18. *Is there a role for device-based therapy for the treatment of hypertension?* A number of device-based interventions have been developed and studied for the treatment of hypertension. To date, the results from these studies have not provided sufficient evidence to recommend their routine use. Consequently, the use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available.
19. *Managing cardiovascular disease risk in hypertensive patients beyond BP: statins.* For hypertensive patients at moderate CVD risk or higher, or those with established CVD, BP lowering alone will not optimally reduce their risk. These patients would also benefit from statin therapy, which further reduces the risk of a myocardial infarction by approximately one-third and stroke by approximately one-quarter, even when BP is controlled. Similar benefits have been seen in hypertensive patients at the border between low and moderaterisk. Thus, many more hypertensive patients would benefit from statin therapy than are currently receiving this treatment.
20. *Managing cardiovascular disease risk in hypertensive patients beyond BP: antiplatelet therapy.* Antiplatelet therapy, especially low-dose aspirin, is recommended for secondary prevention in hypertensive patients, but is not recommended for primary prevention (i.e. in patients without CVD).

**'WHAT TO DO' AND 'WHAT NOT TO DO' MESSAGES FROM THE GUIDELINES**

| <b>Recommendations</b>                                                                                                                                                                                                                                                                                                                                                                                                                       | <b>Class<sup>a</sup></b> | <b>Level<sup>b</sup></b> |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|
| <b>Classification of BP</b>                                                                                                                                                                                                                                                                                                                                                                                                                  |                          |                          |
| It is recommended that BP be classified as optimal, normal, or high-normal, or grades 1–3 hypertension, according to office BP.                                                                                                                                                                                                                                                                                                              | <b>I</b>                 | <b>C</b>                 |
| <b>Screening for hypertension</b>                                                                                                                                                                                                                                                                                                                                                                                                            |                          |                          |
| Screening programmes for hypertension are recommended. All adults ( $\geq 18$ years) should have their office BP measured and recorded in their medical file, and be aware of their BP.                                                                                                                                                                                                                                                      | <b>I</b>                 | <b>B</b>                 |
| <b>Diagnosis of hypertension</b>                                                                                                                                                                                                                                                                                                                                                                                                             |                          |                          |
| It is recommended to base the diagnosis of hypertension on:                                                                                                                                                                                                                                                                                                                                                                                  | <b>I</b>                 | <b>C</b>                 |
| <ul style="list-style-type: none"> <li>■ Repeated office BP measurements on more than one visit, except when hypertension is severe (e.g. grade 3 and especially in high-risk patients). At each visit, three BP measurements should be recorded, 1–2 min apart, and additional measurements performed if the first two readings differ by <math>&gt;10</math> mmHg. The patient's BP is the average of the last two BP readings.</li> </ul> |                          |                          |
| OR                                                                                                                                                                                                                                                                                                                                                                                                                                           |                          |                          |
| <ul style="list-style-type: none"> <li>■ Out-of-office BP measurement with ABPM and/or HBPM, provided that these measurements are logistically and economically feasible.</li> </ul>                                                                                                                                                                                                                                                         | <b>I</b>                 | <b>C</b>                 |
| <b>Office BP thresholds for the initiation of drug treatment for hypertension</b>                                                                                                                                                                                                                                                                                                                                                            |                          |                          |
| Prompt initiation of BP-lowering drug treatment is recommended in patients with grade 2 or 3 hypertension at any level of CV risk, simultaneously with the initiation of lifestyle changes.                                                                                                                                                                                                                                                  | <b>I</b>                 | <b>A</b>                 |
| In patients with grade 1 hypertension:                                                                                                                                                                                                                                                                                                                                                                                                       | <b>I</b>                 | <b>B</b>                 |
| <ul style="list-style-type: none"> <li>■ Lifestyle interventions are recommended to determine if this will normalize BP.</li> </ul>                                                                                                                                                                                                                                                                                                          |                          |                          |
| <ul style="list-style-type: none"> <li>■ In patients with grade 1 hypertension at low-moderate-risk and without evidence of HMOD, BP-lowering drug treatment is recommended if the patient remains hypertensive after a period of lifestyle intervention.<sup>c</sup></li> </ul>                                                                                                                                                             | <b>I</b>                 | <b>A</b>                 |
| <ul style="list-style-type: none"> <li>■ In patients with grade 1 hypertension at high risk or with evidence of HMOD, prompt initiation of drug treatment is recommended simultaneously with lifestyle interventions.</li> </ul>                                                                                                                                                                                                             | <b>I</b>                 | <b>A</b>                 |
| In fit older patients with hypertension (even if aged $>80$ years), BP-lowering drug treatment and lifestyle intervention are recommended when SBP is $\geq 160$ mmHg.                                                                                                                                                                                                                                                                       | <b>I</b>                 | <b>A</b>                 |
| BP-lowering drug treatment and lifestyle intervention are recommended in fit older patients ( $>65$ years but not $>80$ years) when SBP is in the grade 1 range (140–159 mmHg), provided that treatment is well tolerated.                                                                                                                                                                                                                   | <b>I</b>                 | <b>A</b>                 |
| In patients with high-normal BP (130–139/85–89 mmHg), lifestyle changes are recommended.                                                                                                                                                                                                                                                                                                                                                     | <b>I</b>                 | <b>A</b>                 |
| Withdrawal of BP-lowering drug treatment on the basis of age, even when patients attain an age of $\geq 80$ years, is not recommended, provided that treatment is well tolerated.                                                                                                                                                                                                                                                            | <b>III</b>               | <b>A</b>                 |
| <b>Office BP treatment targets</b>                                                                                                                                                                                                                                                                                                                                                                                                           |                          |                          |
| It is recommended that the first objective of treatment should be to lower BP to $<140/90$ mmHg in all patients, and provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients.                                                                                                                                                                                           | <b>I</b>                 | <b>A</b>                 |
| In patients $<65$ years receiving BP-lowering drugs, it is recommended that SBP should be lowered to a BP range of 120–129 mmHg in most patients. <sup>d</sup>                                                                                                                                                                                                                                                                               | <b>I</b>                 | <b>A</b>                 |
| In older patients (aged $\geq 65$ years) receiving BP-lowering drugs, it is recommended that SBP should be targeted to a BP range of 130–139 mmHg.                                                                                                                                                                                                                                                                                           | <b>I</b>                 | <b>A</b>                 |
| <b>Treatment of hypertension: lifestyle interventions</b>                                                                                                                                                                                                                                                                                                                                                                                    |                          |                          |
| Salt restriction to $<5$ g per day is recommended.                                                                                                                                                                                                                                                                                                                                                                                           | <b>I</b>                 | <b>A</b>                 |
| It is recommended to restrict alcohol consumption to $<14$ units per week for men and $<8$ units per week for women.                                                                                                                                                                                                                                                                                                                         | <b>I</b>                 | <b>A</b>                 |
| Increased consumption of vegetables, fresh fruits, fish, nuts, unsaturated fatty acids (olive oil); low consumption of red meat; and consumption of low-fat dairy products are recommended.                                                                                                                                                                                                                                                  | <b>I</b>                 | <b>A</b>                 |
| Body weight control is indicated to avoid obesity (BMI $>30$ kg/m <sup>2</sup> , or waist circumference $>102$ cm in men and $>88$ cm in women) and aim for healthy BMI (about 20–25 kg/m <sup>2</sup> ) and waist circumference values ( $<94$ cm in men and $<80$ cm in women) to reduce BP and cardiovascular risk.                                                                                                                       | <b>I</b>                 | <b>A</b>                 |

Continued

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |            |          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|----------|
| Regular aerobic exercise (e.g. $\geq 30$ min of moderate dynamic exercise on 5–7 days per week) is recommended.                                                                                                                                                                                                                                                                                                                                                                            | <b>I</b>   | <b>A</b> |
| Smoking cessation and supportive care and referral to smoking cessation programmes are recommended.                                                                                                                                                                                                                                                                                                                                                                                        | <b>I</b>   | <b>B</b> |
| It is recommended to avoid binge drinking.                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <b>III</b> | <b>A</b> |
| <b>Treatment of hypertension: Drug treatment</b>                                                                                                                                                                                                                                                                                                                                                                                                                                           |            |          |
| Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used. It is recommended that beta-blockers are combined with any of the other major drug classes when there are specific clinical situations (e.g. angina, post-myocardial infarction, heart failure, or heart rate control). | <b>I</b>   | <b>A</b> |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <b>I</b>   | <b>A</b> |
| It is recommended to initiate antihypertensive treatment with a two-drug combination, preferably in an SPC. Exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is $<150$ mmHg) [342,346,351].                                                                                                                                                                                                                                    | <b>I</b>   | <b>B</b> |
| It is recommended that if BP is not controlled <sup>a</sup> with a two-drug combination, treatment should be increased to a three-drug combination, usually a RAS blocker with a CCB and thiazide/thiazide-like diuretics, preferably as an SPC.                                                                                                                                                                                                                                           | <b>I</b>   | <b>A</b> |
| It is recommended that if BP is not controlled <sup>a</sup> with a three-drug combination, treatment should be increased by the addition of spironolactone or, if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, a beta-blocker, or an alpha-blocker.                                                                                                                                                                                                | <b>I</b>   | <b>B</b> |
| The combination of two RAS blockers is not recommended.                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>III</b> | <b>A</b> |
| <b>Treatment of hypertension: device-based therapies</b>                                                                                                                                                                                                                                                                                                                                                                                                                                   |            |          |
| Use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available.                                                                                                                                                                                                                                                              | <b>III</b> | <b>B</b> |
| <b>Management of CVD risk in hypertensive patients</b>                                                                                                                                                                                                                                                                                                                                                                                                                                     |            |          |
| Cardiovascular risk assessment with the SCORE system is recommended for hypertensive patients who are not already at high or very high risk due to established CVD, renal disease, or diabetes.                                                                                                                                                                                                                                                                                            | <b>I</b>   | <b>B</b> |
| For patients at high or very high cardiovascular risk, statins are recommended.                                                                                                                                                                                                                                                                                                                                                                                                            | <b>I</b>   | <b>B</b> |
| Antiplatelet therapy, in particular low-dose aspirin, is recommended for secondary prevention in hypertensive patients.                                                                                                                                                                                                                                                                                                                                                                    | <b>I</b>   | <b>A</b> |
| Aspirin is not recommended for primary prevention in hypertensive patients without CVD.                                                                                                                                                                                                                                                                                                                                                                                                    | <b>III</b> | <b>A</b> |
| Routine genetic testing for hypertensive patients is not recommended.                                                                                                                                                                                                                                                                                                                                                                                                                      | <b>III</b> | <b>C</b> |

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; HBPM, home blood pressure monitoring; HMOD, hypertension-mediated organ damage; RAS, renin–angiotensin system; RCT, randomized controlled trial; SBP, systolic blood pressure; SCORE, Systematic COronary Risk Evaluation; SPC, single-pill combination.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

<sup>c</sup> In patients with grade 1 hypertension and low-moderate-risk, drug treatment may be preceded by a prolonged period of lifestyle intervention to determine if this will normalize BP. The duration of the lifestyle intervention alone will depend on the level of BP within the grade 1 range (i.e. the likelihood of achieving BP control with lifestyle intervention alone) and the opportunities for significant lifestyle change in individual patients.

<sup>d</sup> Less evidence is available for this target in low-moderate-risk patients.

<sup>e</sup> Adherence to medication should be checked.

## APPENDIX

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## REFERENCES

1. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: A systematic review and metaanalysis. *JAMA* 2015;313:603–615.
2. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J et al. Blood pressure lowering for prevention of cardiovascular disease and death: A systematic review and meta-analysis. *Lancet* 2016;387:957–967.
3. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mmHg, 1990–2015. *JAMA* 2017;317:165–182.
4. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: A metaanalysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–1913.
5. NCD Risk Factor Collaboration. Worldwide trends in blood pressure from 1975 to 2015: A pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* 2017;389:37–55.
6. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H et al., INTERSTROKE Investigators. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): A case-control study. *Lancet* 2016;388:761–775.
7. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S et al. Blood pressure and incidence of twelve cardiovascular diseases: Lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet* 2014;383:1899–1911.
8. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension. 1. Overview, metaanalyses, and meta-regression analyses of randomized trials. *J Hypertens* 2014;32:2285–2295.
9. Tsai WC, Wu HY, Peng YS, Yang JY, Chen HY, Chiu YL et al. Association of intensive blood pressure control and kidney disease progression in nondiabetic patients with chronic kidney disease: A systematic review and meta-analysis. *JAMA Intern Med* 2017;177:792–799.
10. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F et al., INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet* 2004;364:937–952.

11. Banegas JR, Lopez-Garcia E, Dallongeville J, Guallar E, Halcov JP, Borghi C et al. Achievement of treatment goals for primary prevention of cardiovascular disease in clinical practice across Europe: The EURICA study. *Eur Heart J* 2011;32:2143–2152.
12. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A et al. PURE Study Investigators. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA* 2013;310:959–968.
13. Falaschetti E, Mindell J, Knott C, Poulter N. Hypertension management in England: A serial cross-sectional study from 1994 to 2011. *Lancet* 2014;383:1912–1919.
14. Tocci G, Agabiti Rosei E, Ambrosioni E, Borghi C, Ferri C, Ferrucci A et al. Blood pressure control in Italy: Analysis of clinical data from 2005–2011 surveys on hypertension. *J Hypertens* 2012;30:1065–1074.
15. European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003;21:1011–1053.
16. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007;25:1105–1187.
17. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;34:2159–2219.
18. Lurbe E, Agabiti Rosei E, Cruickshank JK, Dominiczak A, Erdine S, Hirth A et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. *J Hypertens* 2016;34:1887–1920.
19. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: Analysis of worldwide data. *Lancet* 2005;365:217–223.
20. Lip GYH, Coca A, Kahan T, Boriani G, Manolis AS, Olsen MH et al. Hypertension and cardiac arrhythmias: Executive summary of a consensus document from the European Heart Rhythm Association (EHRA) and ESC Council on Hypertension, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). *Eur Heart J Cardiovasc Pharmacother* 2017;3:235–250.
21. Gottesman RF, Albert MS, Alonso A, Coker LH, Coresh J, Davis SM et al. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. *JAMA Neurol* 2017;74:1246–1254.
22. Rovio SP, Pahkala K, Nevalainen J, Juonala M, Salo P, Kahonen M et al. Cardiovascular risk factors from childhood and midlife cognitive performance: The Young Finns study. *J Am Coll Cardiol* 2017;69:2279–2289.
23. Vishram JK, Borglykke A, Andreassen AH, Jeppesen J, Ibsen H, Jorgensen T et al. MORGAM Project. Impact of age on the importance of systolic and diastolic blood pressures for stroke risk: The MOnica, Risk, Genetics, Archiving, and Monograph (MORGAM) project. *Hypertension* 2012;60:1117–1123.
24. Brown DW, Giles WH, Greenlund KJ. Blood pressure parameters and risk of fatal stroke, NHANES II mortality study. *Am J Hypertens* 2007;20:338–341.
25. Lawes CM, Rodgers A, Bennett DA, Parag V, Suh I, Ueshima H, MacMahon S. Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular disease in the Asia Pacific region. *J Hypertens* 2003;21:707–716.
26. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham heart study. *Circulation* 1999;100:354–360.
27. Williams B, Lindholm LH, Sever P. Systolic pressure is all that matters. *Lancet* 2008;371:2219–2221.
28. Domanski M, Mitchell G, Pfeffer M, Neaton JD, Norman J, Svendsen K et al. MRFIT Research Group. Pulse pressure and cardiovascular disease-related mortality: Follow-up study of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 2002;287:2677–2683.
29. Franklin SS, Lopez VA, Wong ND, Mitchell GF, Larson MG, Vasan RS, Levy D. Single versus combined blood pressure components and risk for cardiovascular disease: The Framingham Heart Study. *Circulation* 2009;119:243–250.
30. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL et al. REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006;295:180–189.
31. Mancia G, Facchetti R, Bombelli M, Polo Friz H, Grassi G, Giannattasio C, Sega R. Relationship of office, home, and ambulatory blood pressure to blood glucose and lipid variables in the PAMELA population. *Hypertension* 2005;45:1072–1077.
32. Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A et al. Lifetime risks of cardiovascular disease. *N Engl J Med* 2012;366:321–329.
33. Aktas MK, Ozduran V, Pothier CE, Lang R, Lauer MS. Global risk scores and exercise testing for predicting all-cause mortality in a preventive medicine program. *JAMA* 2004;292:1462–1468.
34. Cooney MT, Dudina AL, Graham IM. Value and limitations of existing scores for the assessment of cardiovascular risk: A review for clinicians. *J Am Coll Cardiol* 2009;54:1209–1227.
35. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL et al. ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;37:2315–2381.
36. Borghi C, Agabiti Rosei E, Bardin T, Dawson J, Dominiczak A, Kielstein JT et al. Serum uric acid and the risk of cardiovascular and renal disease. *J Hypertens* 2015;33:1729–1741;discussion 1741.
37. van Dis I, Geleijnse JM, Boer JM, Kromhout D, Boshuizen H, Grobbee DE et al. Effect of including nonfatal events in cardiovascular risk estimation, illustrated with data from The Netherlands. *Eur J Prev Cardiol* 2014;21:377–383.
38. Cuspidi C, Ambrosioni E, Mancia G, Pessina AC, Trimarco B, Zanchetti A. Role of echocardiography and carotid ultrasonography in stratifying risk in patients with essential hypertension: The Assessment of Prognostic Risk Observational Survey. *J Hypertens* 2002;20:1307–1314.
39. Roman MJ, Pickering TG, Schwartz JE, Pini R, Devereux RB. Association of carotid atherosclerosis and left ventricular hypertrophy. *J Am Coll Cardiol* 1995;25:83–90.
40. Cuspidi C, Valerio C, Sala C, Esposito A, Masaidi M, Negri F et al. Prevalence and correlates of multiple organ damage in a never-treated hypertensive population: Role of ambulatory blood pressure. *Blood Press Monit* 2008;13:7–13.
41. Pontremoli R, Ravera M, Bezante GP, Viazzi F, Nicoletta C, Berruti V et al. Left ventricular geometry and function in patients with essential hypertension and microalbuminuria. *J Hypertens* 1999;17:993–1000.
42. Sehestedt T, Jeppesen J, Hansen TW, Wachtell K, Ibsen H, Torp-Pedersen C et al. Risk prediction is improved by adding markers of subclinical organ damage to SCORE. *Eur Heart J* 2010;31:883–891.
43. Perrone-Filardi P, Coca A, Galderisi M, Paolillo S, Alpendurada F, de Simone G et al. Noninvasive cardiovascular imaging for evaluating subclinical target organ damage in hypertensive patients: A consensus article from the European Association of Cardiovascular Imaging, the European Society of Cardiology Council on Hypertension and the European Society of Hypertension. *J Hypertens* 2017;35:1727–1741.
44. Stergiou GS, Alpert B, Mieke S, Asmar R, Atkins N, Eckert S et al. A universal standard for the validation of blood pressure measuring devices: Association for the Advancement of Medical Instrumentation/European Society of Hypertension/International Organization for Standardization (AAMI/ESH/ISO) Collaboration Statement. *J Hypertens* 2018;36:472–478.
45. Clark CE, Taylor RS, Shore AC, Ukoumunne OC, Campbell JL. Association of a difference in systolic blood pressure between arms with vascular disease and mortality: A systematic review and meta-analysis. *Lancet* 2012;379:905–914.
46. Fagard RH, De Cort P. Orthostatic hypotension is a more robust predictor of cardiovascular events than nighttime reverse dipping in elderly. *Hypertension* 2010;56:56–61.
47. Julius S, Palatini P, Kjeldsen SE, Zanchetti A, Weber MA, McInnes GT et al. Usefulness of heart rate to predict cardiac events in treated patients with high-risk systemic hypertension. *Am J Cardiol* 2012;109:685–692.
48. Myers MG. A short history of automated office blood pressure – 15 years to SPRINT. *J Clin Hypertens (Greenwich)* 2016;18:721–724.
49. Parati G, Pomidossi G, Casadei R, Mancia G. Lack of alerting reactions to intermittent cuff inflations during noninvasive blood pressure monitoring. *Hypertension* 1985;7:597–601.

50. Myers MG, Godwin M, Dawes M, Kiss A, Tobe SW, Kaczorowski J. Measurement of blood pressure in the office: Recognizing the problem and proposing the solution. *Hypertension* 2010;55:195–200.
51. Research Group SPRINT, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;373:2103–2116.
52. Filipovsky J, Seidlerova J, Kratochvil Z, Karnosova P, Hronova M, Mayer O Jr. Automated compared to manual office blood pressure and to home blood pressure in hypertensive patients. *Blood Press* 2016;25:228–234.
53. Myers MG, Kaczorowski J, Dolovich L, Tu K, Paterson JM. Cardiovascular risk in hypertension in relation to achieved blood pressure using automated office blood pressure measurement. *Hypertension* 2016;68:866–872.
54. Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G et al. European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability. European Society of Hypertension practice guidelines for ambulatory Blood Pressure monitoring. *J Hypertens* 2014;32:1359–1366.
55. Stergiou GS, Parati G, Vlachopoulos C, Achimastos A, Andreadis E, Asmar R et al. Methodology and technology for peripheral and central blood pressure and blood pressure variability measurement: Current status and future directions – Position statement of the European Society of Hypertension Working Group on blood pressure monitoring and cardiovascular variability. *J Hypertens* 2016;34:1665–1677.
56. O'Brien E, Parati G, Stergiou G, Asmar R, Beilin L, Bilo G et al. European Society of Hypertension Working Group on Blood Pressure M. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens* 2013;31:1731–1768.
57. Parati G, Stergiou GS, Asmar R, Bilo G, de Leeuw P, Imai Y et al. European Society of Hypertension guidelines for blood pressure monitoring at home: A summary report of the Second International Consensus Conference on Home Blood Pressure Monitoring. *J Hypertens* 2008;26:1505–1526.
58. Bliziotis IA, Destounis A, Stergiou GS. Home versus ambulatory and office blood pressure in predicting target organ damage in hypertension: A systematic review and meta-analysis. *J Hypertens* 2012;30:1289–1299.
59. Ward AM, Takahashi O, Stevens R, Heneghan C. Home measurement of blood pressure and cardiovascular disease: Systematic review and meta-analysis of prospective studies. *J Hypertens* 2012;30:449–456.
60. McManus RJ, Mant J, Bray EP, Holder R, Jones MI, Greenfield S et al. Telemonitoring and self-management in the control of hypertension (TASMINH2): A randomised controlled trial. *Lancet* 2010;376:163–172.
61. McManus RJ, Mant J, Haque MS, Bray EP, Bryan S, Greenfield SM et al. Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: The TASMIN-SR randomized clinical trial. *JAMA* 2014;312:799–808.
62. Tucker KL, Sheppard JP, Stevens R, Bosworth HB, Bove A, Bray EP et al. Self-monitoring of blood pressure in hypertension: A systematic review and individual patient data meta-analysis. *PLoS Med* 2017;14:e1002389.
63. Omboni S, Gazzola T, Carabelli G, Parati G. Clinical usefulness and cost effectiveness of home blood pressure telemonitoring: Metaanalysis of randomized controlled studies. *J Hypertens* 2013;31:455–467;discussion 467–458.
64. Parati G, Omboni S. Role of home blood pressure telemonitoring in hypertension management: An update. *Blood Press Monit* 2010;15:285–295.
65. Gaborieau V, Delarche N, Gosse P. Ambulatory blood pressure monitoring versus self-measurement of blood pressure at home: Correlation with target organ damage. *J Hypertens* 2008;26:1919–1927.
66. Clement DL, De Buyzere ML, De Bacquer DA, de Leeuw PW, Duprez DA, Fagard RH et al. Office versus Ambulatory Pressure Study Investigators. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med* 2003;348:2407–2415.
67. Segal R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: Follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation* 2005;111:1777–1783.
68. Banegas JR, Ruilope LM, de la Sierra A, Vinyoles E, Gorostidi M, de la Cruz JJ et al. Relationship between clinic and ambulatory blood-pressure measurements and mortality. *N Engl J Med* 2018;378:1509–1520.
69. Investigators ABC-H, Roush GC, Fagard RH, Salles GF, Pierdomenico SD, Reboldi G et al. Prognostic impact from clinic, daytime, and night-time systolic blood pressure in nine cohorts of 13,844 patients with hypertension. *J Hypertens* 2014;32:2332–2340;discussion 2340.
70. Fagard RH, Celis H, Thijs L, Staessen JA, Clement DL, De Buyzere ML, De Bacquer DA. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension* 2008;51:55–61.
71. Parati G, Ochoa JE, Bilo G, Agarwal R, Covic A, Dekker FW et al., European Renal and Cardiovascular Medicine Working Group of the European Renal Association-Eurodialysis and Transplant Association. Hypertension in chronic kidney disease part 2: Role of ambulatory and home blood pressure monitoring for assessing alterations in blood pressure variability and blood pressure profiles. *Hypertension* 2016;67:1102–1110.
72. Piper MA, Evans CV, Burda BU, Margolis KL, O'Connor E, Whitlock EP. Diagnostic and predictive accuracy of blood pressure screening methods with consideration of rescreening intervals: A systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2015;162:192–204.
73. Omboni S, Parati G, Palatini P, Vanasia A, Muiesan ML, Cuspidi C, Mancia G. Reproducibility and clinical value of nocturnal hypotension: Prospective evidence from the SAMPLE study. Study on Ambulatory Monitoring of Pressure and Lisinopril Evaluation. *J Hypertens* 1998;16:733–738.
74. Mancia G, Verdecchia P. Clinical value of ambulatory blood pressure: evidence and limits. *Circ Res* 2015;116:1034–1045.
75. Salles GF, Reboldi G, Fagard RH, Cardoso CR, Pierdomenico SD, Verdecchia P et al. ABC-H Investigators. Prognostic effect of the nocturnal blood pressure fall in hypertensive patients: The Ambulatory Blood Pressure Collaboration in patients with Hypertension (ABC-H) meta-analysis. *Hypertension* 2016;67:693–700.
76. Mancia G. Short-and long-term blood pressure variability: Present and future. *Hypertension* 2012;60:512–517.
77. Kario K, Pickering TG, Umeda Y, Hoshida S, Hoshida Y, Morinari M et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: A prospective study. *Circulation* 2003;107:1401–1406.
78. Parati G, Schillaci G. What are the real determinants of the ambulatory arterial stiffness index?. *J Hypertens* 2012;30:472–476.
79. Kikuya M, Ohkubo T, Metoki H, Asayama K, Hara A, Obara T et al. Day-by-day variability of blood pressure and heart rate at home as a novel predictor of prognosis: The Ohasama study. *Hypertension* 2008;52:1045–1050.
80. Mancia G, Zanchetti A. White-coat hypertension: Misnomers, misconceptions and misunderstandings. What should we do next? *J Hypertens* 1996;14:1049–1052.
81. Bobrie G, Clerson P, Menard J, Postel-Vinay N, Chatellier G, Plouin PF. Masked hypertension: A systematic review. *J Hypertens* 2008;26:1715–1725.
82. Mancia G, Bombelli M, Cuspidi C, Facchetti R, Grassi G. Cardiovascular risk associated with white-coat hypertension: Pro side of the argument. *Hypertension* 2017;70:668–675.
83. Parati G, Omboni S, Staessen J, Thijs L, Fagard R, Ulian L, Mancia G. Limitations of the difference between clinic and daytime blood pressure as a surrogate measure of the 'white-coat' effect. Syst-Eur investigators. *J Hypertens* 1998;16:23–29.
84. Banegas JR, Ruilope LM, de la Sierra A, de la Cruz JJ, Gorostidi M, Segura J et al. High prevalence of masked uncontrolled hypertension in people with treated hypertension. *Eur Heart J* 2014;35:3304–3312.
85. Huang Y, Huang W, Mai W, Cai X, An D, Liu Z et al. White-coat hypertension is a risk factor for cardiovascular diseases and total mortality. *J Hypertens* 2017;35:677–688.
86. Briassoulis A, Androulakis E, Palla M, Papageorgiou N, Tousoulis D. White-coat hypertension and cardiovascular events: A meta-analysis. *J Hypertens* 2016;34:593–599.
87. Grassi G, Seravalle G, Trevano FQ, Dell'oro R, Bolla G, Cuspidi C et al. Neurogenic abnormalities in masked hypertension. *Hypertension* 2007;50:537–542.
88. Mancia G. Clinical significance of white-coat hypertension. *J Hypertens* 2016;34:623–626.
89. Mancia G. White-coat hypertension: Growing evidence in favour of its adverse prognostic significance. *J Hypertens* 2017;35:710–712.



90. Mancia G, Grassi G. The heterogeneous nature of white-coat hypertension. *J Am Coll Cardiol* 2016;68:2044–2046.
91. Asayama K, Li Y, Franklin SS, Thijs L, O'Brien E, Staessen JA. Cardiovascular risk associated with white-coat hypertension: Con side of the argument. *Hypertension* 2017;70:676–682.
92. Lurbe E, Torro I, Alvarez V, Nawrot T, Paya R, Redon J, Staessen JA. Prevalence, persistence, and clinical significance of masked hypertension in youth. *Hypertension* 2005;45:493–498.
93. Mancia G, Facchetti R, Bombelli M, Grassi G, Sega R. Long-term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure. *Hypertension* 2006;47:846–853.
94. Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B et al. Cardiovascular prognosis of 'masked hypertension' detected by blood pressure self-measurement in elderly treated hypertensive patients. *JAMA* 2004;291:1342–1349.
95. Fagard RH, Cornelissen VA. Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normotension: A meta-analysis. *J Hypertens* 2007;25:2193–2198.
96. Franklin SS, Thijs L, Li Y, Hansen TW, Boggia J, Liu Y et al. Response to masked hypertension in untreated and treated patients with diabetes mellitus: Attractive but questionable interpretations and response to Is masked hypertension related to diabetes mellitus?. *Hypertension* 2013;62:e23–e25.
97. Lurbe E, Redon J, Kesani A, Pascual JM, Tacons J, Alvarez V, Battie D. Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. *New Engl J Med* 2002;347:797–805.
98. Lindholt JS, Sogaard R. Population screening and intervention for vascular disease in Danish men (VIVA): A randomised controlled trial. *Lancet* 2017;390:2256–2265.
99. Hodgkinson J, Mant J, Martin U, Guo B, Hobbs FD, Deeks JJ et al. Relative effectiveness of clinic and home blood pressure monitoring compared with ambulatory blood pressure monitoring in diagnosis of hypertension: Systematic review. *BMJ* 2011;342:d3621.
100. Vinyoles E, Felip A, Pujol E, de la Sierra A, Dura R, del Rey RH et al. Clinical characteristics of isolated clinic hypertension. *J Hypertens* 2008;26:438–445.
101. McManus RJ, Mant J. Do differences in blood pressure between arms matter?. *Lancet* 2012;379:872–873.
102. McManus RJ, Mant J, Franssen M, Nickless A, Schwartz C, Hodgkinson J et al. Efficacy of self-monitored blood pressure, with or without telemonitoring, for titration of antihypertensive medication (TASMINH4): An unmasked randomised controlled trial. *Lancet* 2018;391:949–959.
103. Le VV, Mitiku T, Sungar G, Myers J, Froelicher V. The blood pressure response to dynamic exercise testing: A systematic review. *Prog Cardiovasc Dis* 2008;51:135–160.
104. Holmqvist L, Mortensen L, Kanckos C, Ljungman C, Mehlig K, Manhem K. Exercise blood pressure and the risk of future hypertension. *J Hum Hypertens* 2012;26:691–695.
105. Parati G, Agostoni P, Basnyat B, Bilo G, Brugger H, Coca A et al. Clinical recommendations for high altitude exposure of individuals with preexisting cardiovascular conditions. *Eur Heart J* 2018;39:1546–1554.
106. Picone DS, Schultz MG, Otahal P, Aakhus S, Al-Jumaily AM, Black JA et al. Accuracy of cuff-measured blood pressure: Systematic reviews and meta-analyses. *J Am Coll Cardiol* 2017;70:572–586.
107. Herbert A, Cruickshank JK, Laurent S, Boutouyrie P. Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk factors. *Eur Heart J* 2014;35:3122–3133.
108. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D et al. CAFE Investigators, Anglo-Scandinavian Cardiac Outcomes Trial Investigators, CAFE Steering Committee and Writing Committee. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: Principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006;113:1213–1225.
109. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: A systematic review and meta-analysis. *Eur Heart J* 2010;31:1865–1871.
110. Lurbe E, Redon J. Isolated systolic hypertension in young people is not spurious and should be treated: Con side of the argument. *Hypertension* 2016;68:276–280.
111. McEniery CM, Franklin SS, Cockcroft JR, Wilkinson IB. Isolated systolic hypertension in young people is not spurious and should be treated: Pro side of the argument. *Hypertension* 2016;68:269–275.
112. Devereux RB, Alderman MH. Role of preclinical cardiovascular disease in the evolution from risk factor exposure to development of morbid events. *Circulation* 1993;88:1444–1455.
113. Cordero A, Morillas P, Bertomeu-Gonzalez V, Quiles J, Mazon P, Guindo J et al. Prevalence of Peripheral Arterial Disease in Patients with Acute Coronary Syndrome Investigators. Clustering of target organ damage increases mortality after acute coronary syndromes in patients with arterial hypertension. *J Hum Hypertens* 2011;25:600–607.
114. Greve SV, Blicher MK, Sehestedt T, Gram-Kampmann EM, Rasmussen S, Vishram JK, Olsen MH. Effective risk stratification in patients with moderate cardiovascular risk using albuminuria and atherosclerotic plaques in the carotid arteries. *J Hypertens* 2015;33:1563–1570.
115. de Simone G, Devereux RB, Izzo R, Giffoglio D, Lee ET, Howard BV, Roman MJ. Lack of reduction of left ventricular mass in treated hypertension: The strong heart study. *J Am Heart Assoc* 2013;2:e000144.
116. Lonnebakken MT, Izzo R, Mancusi C, Gerdtts E, Losi MA, Cancelliello G et al. Left ventricular hypertrophy regression during antihypertensive treatment in an outpatient clinic (the Campania Salute Network). *J Am Heart Assoc* 2017;6:e004152.
117. Volpe M, Battistoni A, Tocci G, Agabiti Rosei E, Catapano AL, Coppo R et al. Cardiovascular risk assessment beyond systemic coronary risk estimation: A role for organ damage markers. *J Hypertens* 2012;30:1056–1064.
118. Bacharova L, Schocken D, Estes EH, Strauss D. The role of ECG in the diagnosis of left ventricular hypertrophy. *Curr Cardiol Rev* 2014;10:257–261.
119. Pahor M, Guralnik JM, Ambrosius WT, Blair S, Bonds DE, Church TS et al. Effect of structured physical activity on prevention of major mobility disability in older adults: The LIFE study randomized clinical trial. *JAMA* 2014;311:2387–2396.
120. Lehtonen AO, Puukka P, Varis J, Porthan K, Tikkanen JT, Nieminen MS et al. Prevalence and prognosis of ECG abnormalities in normotensive and hypertensive individuals. *J Hypertens* 2016;34:959–966.
121. Okin PM, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS et al. LIFE Study Investigators. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. *JAMA* 2004;292:2343–2349.
122. Okin PM, Oikarinen L, Viitasalo M, Toivonen L, Kjeldsen SE, Nieminen MS et al. LIFE Study Investigators. Prognostic value of changes in the electrocardiographic strain pattern during antihypertensive treatment: The Losartan Intervention for End-Point Reduction in Hypertension Study (LIFE). *Circulation* 2009;119:1883–1891.
123. de Simone G, Izzo R, Chinali M, De Marco M, Casalnuovo G, Rozza F et al. Does information on systolic and diastolic function improve prediction of a cardiovascular event by left ventricular hypertrophy in arterial hypertension? *Hypertension* 2010;56:99–104.
124. Bombelli M, Facchetti R, Cuspidi C, Villa P, Dozio D, Brambilla G et al. Prognostic significance of left atrial enlargement in a general population: Results of the PAMELA study. *Hypertension* 2014;64:1205–1211.
125. Devereux RB, Wachtell K, Gerdtts E, Boman K, Nieminen MS, Papademetriou V et al. Prognostic significance of left ventricular mass change during treatment of hypertension. *JAMA* 2004;292:2350–2356.
126. de Simone G, Izzo R, Aurigemma GP, De Marco M, Rozza F, Trimarco V et al. Cardiovascular risk in relation to a new classification of hypertensive left ventricular geometric abnormalities. *J Hypertens* 2015;33:745–754;discussion 754.
127. Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M et al. Recommendations on the use of echocardiography in adult hypertension: A report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). *Eur Heart J Cardiovasc Imaging* 2015;16:577–605.
128. Gerdtts E, Wachtell K, Omvik P, Otterstad JE, Oikarinen L, Boman K et al. Left atrial size and risk of major cardiovascular events during antihypertensive treatment: Losartan intervention for endpoint reduction in hypertension trial. *Hypertension* 2007;49:311–316.
129. Muiesan ML, Salvetti M, Monteduro C, Bonzi B, Paini A, Viola S et al. Left ventricular concentric geometry during treatment adversely affects cardiovascular prognosis in hypertensive patients. *Hypertension* 2004;43:731–738.

130. Takeuchi M, Nishikage T, Mor-Avi V, Sugeng L, Weinert L, Nakai H et al. Measurement of left ventricular mass by real-time three-dimensional echocardiography: Validation against magnetic resonance and comparison with two-dimensional and m-mode measurements. *J Am Soc Echocardiogr* 2008;21:1001–1005.
131. Stanton T, Jenkins C, Haluska BA, Marwick TH. Association of outcome with left ventricular parameters measured by two-dimensional and three-dimensional echocardiography in patients at high cardiovascular risk. *J Am Soc Echocardiogr* 2014;27:65–73.
132. Codella NC, Lee HY, Fieno DS, Chen DW, Hurtado-Rua S, Kochar M et al. Improved left ventricular mass quantification with partial voxel interpolation: In vivo and necropsy validation of a novel cardiac MRI segmentation algorithm. *Circ Cardiovasc Imaging* 2012;5:137–146.
133. Weinsaft JW, Cham MD, Janik M, Min JK, Henschke CI, Yankelevitz DF, Devereux RB. Left ventricular papillary muscles and trabeculae are significant determinants of cardiac MRI volumetric measurements: Effects on clinical standards in patients with advanced systolic dysfunction. *Int J Cardiol* 2008;126:359–365.
134. Perrone-Filardi P, Coca A, Galderisi M, Paolillo S, Alpendurada F, de Simone G et al. Noninvasive cardiovascular imaging for evaluating subclinical target organ damage in hypertensive patients: A consensus paper from the European Association of Cardiovascular Imaging (EACVI), the European Society of Cardiology Council on Hypertension, and the European Society of Hypertension (ESH). *Eur Heart J Cardiovasc Imaging* 2017;18:945–960.
135. de Simone G, Kitzman DW, Chinali M, Oberman A, Hopkins PN, Rao DC et al. Left ventricular concentric geometry is associated with impaired relaxation in hypertension: The HyperGEN study. *Eur Heart J* 2005;26:1039–1045.
136. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129–2200.
137. Yaghi S, Moon YP, Mora-McLaughlin C, Willey JZ, Cheung K, Di Tullio MR et al. Left atrial enlargement and stroke recurrence: The Northern Manhattan Stroke Study. *Stroke* 2015;46:1488–1493.
138. Losi MA, Izzo R, De Marco M, Canciello G, Rapacciuolo A, Trimarco V et al. Cardiovascular ultrasound exploration contributes to predict incident atrial fibrillation in arterial hypertension: The Campania Salute Network. *Int J Cardiol* 2015;199:290–295.
139. Douglas PS. The left atrium: A biomarker of chronic diastolic dysfunction and cardiovascular disease risk. *J Am Coll Cardiol* 2003;42:1206–1207.
140. Kuznetsova T, Haddad F, Tikhonoff V, Kloch-Badelek M, Ryabikov A, Knez J et al. European Project On Genes in Hypertension Investigators. Impact and pitfalls of scaling of left ventricular and atrial structure in population-based studies. *J Hypertens* 2016;34:1186–1194.
141. Evangelista A, Flachskampf FA, Erbel R, Antonini-Canterin F, Vlachopoulos C, Rocchi G et al. European Association of Echocardiography, Document Reviewers: Pepi M, Breithardt OA, Plonska-Gosciniak E. Echocardiography in aortic diseases: EAE recommendations for clinical practice. *Eur J Echocardiogr* 2010;11:645–658.
142. Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: The ARIC (Atherosclerosis Risk In Communities) study. *J Am Coll Cardiol* 2010;55:1600–1607.
143. Vlachopoulos C, Xaplanteris P, Aboyans V, Brodmann M, Cifkova R, Cosentino F et al. The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: Endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. *Atherosclerosis* 2015;241:507–532.
144. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Desvarieux M et al. Advisory Board of the 3rd Watching the Risk Symposium 2004, 13th European Stroke Conference. Mannheim intima-media thickness consensus. *Cerebrovasc Dis* 2004;18:346–349.
145. Inaba Y, Chen JA, Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: A meta-analysis. *Atherosclerosis* 2012;220:128–133.
146. Zanchetti A, Hennig M, Hollweck R, Bond G, Tang R, Cuspidi C et al. Baseline values but not treatment-induced changes in carotid intima-media thickness predict incident cardiovascular events in treated hypertensive patients: Findings in the European Lacidipine Study on Atherosclerosis (ELSA). *Circulation* 2009;120:1084–1090.
147. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB Sr. Carotid-wall intima-media thickness and cardiovascular events. *N Engl J Med* 2011;365:213–221.
148. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D et al. European Network for Non invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: Methodological issues and clinical applications. *Eur Heart J* 2006;27:2588–2605.
149. Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T et al. Artery Society, European Society of Hypertension Working Group on Vascular Structure and Function, European Network for Noninvasive Investigation of Large Arteries. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens* 2012;30:445–448.
150. Reference Values for Arterial Stiffness Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J* 2010;31:2338–2350.
151. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ et al. Aortic pulse wave velocity improves cardiovascular event prediction: An individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol* 2014;63:636–646.
152. Feringa HH, Bax JJ, van Waning VH, Boersma E, Elhendy A, Schouten O et al. The long-term prognostic value of the resting and postexercise ankle-brachial index. *Arch Intern Med* 2006;166:529–535.
153. Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: A meta-analysis. *JAMA* 2008;300:197–208.
154. De Buyzere ML, Clement DL. Management of hypertension in peripheral arterial disease. *Prog Cardiovasc Dis* 2008;50:238–263.
155. Clase CM, Barzilay J, Gao P, Smyth A, Schmieder RE, Tobe S et al. Acute change in glomerular filtration rate with inhibition of the renin-angiotensin system does not predict subsequent renal and cardiovascular outcomes. *Kidney Int* 2017;91:683–690.
156. Schmidt M, Mansfield KE, Bhaskaran K, Nitsch D, Sørensen HT, Smeeth L, Tomlinson LA. Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks: Cohort study. *BMJ* 2017;356:j791.
157. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF III, Feldman HI et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–612.
158. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B et al. HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001;286:421–426.
159. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int* 2013;3:1–150.
160. McTaggart MP, Newall RG, Hirst JA, Bankhead CR, Lamb EJ, Roberts NW, Price CP. Diagnostic accuracy of point-of-care tests for detecting albuminuria: A systematic review and meta-analysis. *Ann Intern Med* 2014;160:550–557.
161. Breslin DJ, Gifford RW Jr, Fairbairn JF 2nd, Kearns TP. Prognostic importance of ophthalmoscopic findings in essential hypertension. *JAMA* 1966;195:335–338.
162. Frant R, Groen J. Prognosis of vascular hypertension; a 9 year followup study of 418 cases. *Arch Intern Med (Chic)* 1950;85:727–750.
163. Sairenchi T, Iso H, Yamagishi K, Irie F, Okubo Y, Gunji J et al. Mild retinopathy is a risk factor for cardiovascular mortality in Japanese with and without hypertension: The Ibaraki Prefectural Health Study. *Circulation* 2011;124:2502–2511.
164. Dimmitt SB, West JN, Eames SM, Gibson JM, Gosling P, Littler WA. Usefulness of ophthalmoscopy in mild to moderate hypertension. *Lancet* 1989;1:1103–1106.
165. Muijsan ML, Salvetti M, Di Castelnuovo A, Paini A, Assanelli D, Costanzo S et al. Moli-sani Study Investigators. Obesity and ECG left ventricular hypertrophy. *J Hypertens* 2017;35:162–169.
166. Longstreth WT Jr, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA et al. Clinical correlates of white matter findings on



- cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke* 1996;27:1274–1282.
167. Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: A systematic review. *Lancet Neurol* 2007;6:611–619.
  168. Iadecola C, Yaffe K, Biller J, Bratzke LC, Faraci FM, Gorelick PB et al. American Heart Association Council on Hypertension, Council on Clinical Cardiology, Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Quality of Care and Outcomes Research, Stroke Council. Impact of hypertension on cognitive function: A scientific statement from the American Heart Association. *Hypertension* 2016;68:e67–e94.
  169. Kearney-Schwartz A, Rossignol P, Bracard S, Felblinger J, Fay R, Boivin JM et al. Vascular structure and function is correlated to cognitive performance and white matter hyperintensities in older hypertensive patients with subjective memory complaints. *Stroke* 2009;40:1229–1236.
  170. Tsoi KK, Chan JY, Hirai HW, Wong SY, Kwok TC. Cognitive tests to detect dementia: A systematic review and meta-analysis. *JAMA Intern Med* 2015;175:1450–1458.
  171. Kato Y, Suzuki S, Uejima T, Semba H, Yamashita T. Variable prognostic value of blood pressure response to exercise. *J Cardiol* 2018;71:31–35.
  172. Bang CN, Devereux RB, Okin PM. Regression of electrocardiographic left ventricular hypertrophy or strain is associated with lower incidence of cardiovascular morbidity and mortality in hypertensive patients independent of blood pressure reduction: a LIFE review. *J Electrocardiol* 2014;47:630–635.
  173. Fagard RH, Celis H, Thijs L, Wouters S. Regression of left ventricular mass by antihypertensive treatment: A meta-analysis of randomized comparative studies. *Hypertension* 2009;54:1084–1091.
  174. Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE et al. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: Losartan intervention for endpoint reduction in hypertension study. *Hypertension* 2005;45:198–202.
  175. Bakris GL, Sarafidis PA, Weir MR, Dahlof B, Pitt B, Jamerson K et al. ACCOMPLISH Trial Investigators. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): A prespecified secondary analysis of a randomised controlled trial. *Lancet* 2010;375:1173–1181.
  176. Haller H, Ito S, Izzo JL Jr, Januszewicz A, Katayama S, Menne J et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med* 2011;364:907–917.
  177. Holtkamp FA, de Zeeuw D, de Graeff PA, Laverman GD, Berl T, Remuzzi G et al. Albuminuria and blood pressure, independent targets for cardioprotective therapy in patients with diabetes and nephropathy: A post hoc analysis of the combined RENAAL and IDNT trials. *Eur Heart J* 2011;32:1493–1499.
  178. Inker LA, Levey AS, Pandya K, Stoycheff N, Okparavero A, Greene T. Early change in proteinuria as a surrogate end point for kidney disease progression: An individual patient meta-analysis. *Am J Kidney Dis* 2014;64:74–85.
  179. de Galan BE, Perkovic V, Ninomiya T, Pillai A, Patel A, Cass A et al. Lowering blood pressure reduces renal events in type 2 diabetes. *J Am Soc Nephrol* 2009;20:883–892.
  180. Ninomiya T, Perkovic V, de Galan BE, Zoungas S, Pillai A, Jardine M et al. ADVANCE Collaborative Group. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. *J Am Soc Nephrol* 2009;20:1813–1821.
  181. Chowdhury EK, Langham RG, Ademi Z, Owen A, Krum H, Wing LM et al. Rate of change in renal function and mortality in elderly treated hypertensive patients. *Clin J Am Soc Nephrol* 2015;10:1154–1161.
  182. Matsushita K, Selvin E, Bash LD, Franceschini N, Astor BC, Coresh J. Change in estimated GFR associates with coronary heart disease and mortality. *J Am Soc Nephrol* 2009;20:2617–2624.
  183. Costanzo P, Perrone-Filardi P, Vassallo E, Paolillo S, Cesarano P, Brevetti G, Chiariello M. Does carotid intima-media thickness regression predict reduction of cardiovascular events? A meta-analysis of 41 randomized trials. *J Am Coll Cardiol* 2010;56:2006–2020.
  184. Wang JG, Staessen JA, Li Y, Van Bortel LM, Nawrot T, Fagard R et al. Carotid intima-media thickness and antihypertensive treatment: A meta-analysis of randomized controlled trials. *Stroke* 2006;37:1933–1940.
  185. Izzo R, Losi MA, Stabile E, Lonnebakken MT, Cenciello G, Esposito G et al. Development of left ventricular hypertrophy in treated hypertensive outpatients: The Campania Salute Network. *Hypertension* 2017;69:136–142.
  186. Schmieder RE, Mann JF, Schumacher H, Gao P, Mancia G, Weber MA et al. ONTARGET Investigators. Changes in albuminuria predict mortality and morbidity in patients with vascular disease. *J Am Soc Nephrol* 2011;22:1353–1364.
  187. Verdecchia P, Dagenais G, Healey J, Gao P, Dans AL, Chazova I et al. Blood pressure and other determinants of new-onset atrial fibrillation in patients at high cardiovascular risk in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant subjects with cardiovascular Disease studies. *J Hypertens* 2012;30:1004–1014.
  188. Criqui MH, Ninomiya JK, Wingard DL, Ji M, Fronek A. Progression of peripheral arterial disease predicts cardiovascular disease morbidity and mortality. *J Am Coll Cardiol* 2008;52:1736–1742.
  189. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001;37:1236–1241.
  190. Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Endorsed by: the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J* 2017;39:763–816.
  191. Fagard R, Brugguljan J, Staessen J, Thijs L, Derom C, Thomis M, Vlietinck R. Heritability of conventional and ambulatory blood pressures. A study in twins. *Hypertension* 1995;26:919–924.
  192. Luft FC. Twins in cardiovascular genetic research. *Hypertension* 2001;37:350–356.
  193. Warren HR, Evangelou E, Cabrera CP, Gao H, Ren M, Mifsud B et al. International Consortium of Blood Pressure 1000G Analyses, Bios Consortium, Lifelines Cohort Study, Understanding Society Scientific Group, CHD Exome+ Consortium, ExomeBP Consortium, T2D Genes Consortium, GoT2D Genes Consortium, Cohorts for Heart and Ageing Research in Genome Epidemiology (CHARGE), Consortium BE, International Genomics of Blood Pressure Consortium, Group UBCCBW. Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk. *Nat Genet* 2017;49:403–415.
  194. Burrello J, Monticone S, Buffolo F, Tetti M, Veglio F, Williams TA, Mulatero P. Is there a role for genomics in the management of hypertension? *Int J Mol Sci* 2017;18:1131.
  195. Dominiczak A, Delles C, Padmanabhan S. Genomics and precision medicine for clinicians and scientists in hypertension. *Hypertension* 2017;69:e10–e13.
  196. Zennaro MC, Boulkroun S, Fernandes-Rosa F. An update on novel mechanisms of primary aldosteronism. *J Endocrinol* 2015;224:R63–R77.
  197. Favier J, Amar L, Gimenez-Roqueplo AP. Paraganglioma and pheochromocytoma: From genetics to personalized medicine. *Nat Rev Endocrinol* 2015;11:101–111.
  198. Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH et al. Endocrine Society. Pheochromocytoma and paraganglioma: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2014;99:1915–1942.
  199. NGS in PPGL (NGSnPPGL) Study Group Toledo RA, Burnichon N, Cascon A, Benn DE, Bayley JP et al. Consensus Statement on next-generation sequencing-based diagnostic testing of hereditary pheochromocytomas and paragangliomas. *Nat Rev Endocrinol* 2017;13:233–247.
  200. Plouin PF, Amar L, Dekkers OM, Fassnacht M, Gimenez-Roqueplo AP, Lenders JW et al. Guideline Working Group. European Society of Endocrinology Clinical Practice Guideline for long-term follow-up of patients operated on for a pheochromocytoma or a paraganglioma. *Eur J Endocrinol* 2016;174:G1–G10.
  201. Brunstrom M, Carlberg B. Association of blood pressure lowering with mortality and cardiovascular disease across blood pressure levels: A systematic review and meta-analysis. *JAMA Intern Med* 2018;178:28–36.
  202. Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. *Br Med Bull* 1994;50:272–298.
  203. Lv J, Ehteshami P, Sarnak MJ, Tighiouart H, Jun M, Ninomiya T et al. Effects of intensive blood pressure lowering on the

- progression of chronic kidney disease: A systematic review and meta-analysis. *CMAJ* 2013;185:949–957.
204. Chalmers J, Woodward M, Borghi C, Manolis A, Mancia G. Strategies to meet the need for long-term data. *J Hypertens* 2016;34:1473–1479.
  205. Cirillo M, Terradura-Vagnarelli O, Mancini M, Menotti A, Zanchetti A, Laurenzi M. Cohort profile: The Gubbio Population Study. *Int J Epidemiol* 2014;43:713–720.
  206. Sytkowski PA, D'Agostino RB, Belanger AJ, Kannel WB. Secular trends in long-term sustained hypertension, long-term treatment, and cardiovascular mortality. The Framingham Heart Study 1950 to 1990. *Circulation* 1996;93:697–703.
  207. Zoungas S, Chalmers J, Neal B, Billot L, Li Q, Hirakawa Y et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014;371:1392–1406.
  208. Kjeldsen S, Feldman RD, Lisheng L, Mourad JJ, Chiang CE, Zhang W et al. Updated national and international hypertension guidelines: A review of current recommendations. *Drugs* 2014;74:2033–2051.
  209. Diao D, Wright JM, Cundiff DK, Gueyffier F. Pharmacotherapy for mild hypertension. *Cochrane Database Syst Rev* 2012;8:CD006742.
  210. Zanchetti A, Grassi G, Mancia G. When should antihypertensive drug treatment be initiated and to what levels should systolic blood pressure be lowered? A critical reappraisal. *J Hypertens* 2009;27:923–934.
  211. Sundstrom J, Arima H, Jackson R, Turnbull F, Rahimi K, Chalmers J et al. Blood Pressure-Lowering Treatment Trialists' Collaboration. Effects of blood pressure reduction in mild hypertension: A systematic review and meta-analysis. *Ann Intern Med* 2015;162:184–191.
  212. Lonn EM, Bosch J, Lopez-Jaramillo P, Zhu J, Liu L, Pais P et al. HOPE-3 Investigators. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 2016;374:2009–2020.
  213. Beckett N, Peters R, Leonetti G, Duggan J, Fagard R, Thijs L et al. HYVET Study Group. Subgroup and per-protocol analyses from the Hypertension in the Very Elderly Trial. *J Hypertens* 2014;32:1478–1487.
  214. Benetos A, Bulpitt CJ, Petrovic M, Ungar A, Agabiti Rosei E, Cherubini A et al. An expert opinion from the European Society of Hypertension-European Union Geriatric Medicine Society Working Group on the management of hypertension in very old, frail subjects. *Hypertension* 2016;67:820–825.
  215. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM et al. SPRINT Research Group. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged  $\geq 75$  years: A randomized clinical trial. *JAMA* 2016;315:2673–2682.
  216. Carlberg B. What do we know about the risks of stopping antihypertensive treatment? *J Hypertens* 2014;32:1400–1401.
  217. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence. 12. Effects in individuals with high-normal and normal blood pressure: Overview and metaanalyses of randomized trials. *J Hypertens* 2017;35:2150–2160.
  218. Blood Pressure-Lowering Treatment Trialists' Collaboration Sundstrom J, Arima H, Woodward M, Jackson R, Karmali K, Lloyd-Jones D et al. Blood pressure-lowering treatment based on cardiovascular risk: A meta-analysis of individual patient data. *Lancet* 2014;384:591–598.
  219. Lim GB. Hypertension: Low sodium and DASH diet to lower blood pressure. *Nat Rev Cardiol* 2018;15:68.
  220. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D et al. HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008;358:1887–1898.
  221. Mancia G, Laurent S, Agabiti Rosei E, Ambrosioni E, Burnier M, Caulfield MJ et al. Reappraisal of European guidelines on hypertension management: A European Society of Hypertension Task Force document. *J Hypertens* 2009;27:2121–2158.
  222. Bohm M, Schumacher H, Teo KK, Lonn EM, Mahfoud F, Mann JFE et al. Achieved blood pressure and cardiovascular outcomes in highrisk patients: Results from ONTARGET and TRANSCEND trials. *Lancet* 2017;389:2226–2237.
  223. Kjeldsen SE, Berge E, Bangalore S, Messerli FH, Mancia G, Holzhauer B et al. No evidence for a J-shaped curve in treated hypertensive patients with increased cardiovascular risk: The VALUE trial. *Blood Press* 2016;25:83–92.
  224. Mancia G, Kjeldsen SE, Zappe DH, Holzhauer B, Hua TA, Zanchetti A et al. Cardiovascular outcomes at different on-treatment blood pressures in the hypertensive patients of the VALUE trial. *Eur Heart J* 2016;37:955–964.
  225. Kjeldsen SE, Lund-Johansen P, Nilsson PM, Mancia G. Unattended blood pressure measurements in the systolic blood pressure intervention trial: Implications for entry and achieved blood pressure values compared with other trials. *Hypertension* 2016;67:808–812.
  226. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels – updated overview and meta-analyses of randomized trials. *J Hypertens* 2016;34:613–622.
  227. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering treatment in hypertension: 8. Outcome reductions vs. discontinuations because of adverse drug events – meta-analyses of randomized trials. *J Hypertens* 2016;34:1451–1463.
  228. Tarnow L, Rossing P, Jensen C, Hansen BV, Parving HH. Long-term renoprotective effect of nisoldipine and lisinopril in type 1 diabetic patients with diabetic nephropathy. *Diabetes Care* 2000;23:1725–1730.
  229. Patel A, ADVANCE Collaborative Group Mac Mahon S, Chalmers J, Neal B, Woodward M, Billot L et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): A randomised controlled trial. *Lancet* 2007;370:829–840.
  230. Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575–1585.
  231. Brunstrom M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: Systematic review and meta-analyses. *BMJ* 2016;352:i717.
  232. Bangalore S, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: Observations from traditional and bayesian random-effects metaanalyses of randomized trials. *Circulation* 2011;123:2799–2810;9 p following 2810.
  233. Black HR, Elliott WJ, Grandits G, Grambsch P, Lucente T, White WB et al. CONVINCE Research Group. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. *JAMA* 2003;289:2073–2082.
  234. Steptoe A, Breeze E, Banks J, Nazroo J. Cohort profile: The English longitudinal study of ageing. *Int J Epidemiol* 2013;42:1640–1648.
  235. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 – Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. *J Hypertens* 2017;35:922–944.
  236. Margolis KL, O'Connor PJ, Morgan TM, Buse JB, Cohen RM, Cushman WC et al. Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: The ACCORD randomized trial. *Diabetes Care* 2014;37:1721–1728.
  237. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998;351:1755–1762.
  238. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;317:703–713.
  239. Mancia G, Messerli F, Bakris G, Zhou Q, Champion A, Pepine CJ. Blood pressure control and improved cardiovascular outcomes in the International Verapamil SR-Trandolapril Study. *Hypertension* 2007;50:299–305.
  240. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 2010;375:895–905.
  241. Mancia G, Schumacher H, Bohm M, Redon J, Schmieder RE, Verdecchia P et al. Relative and combined prognostic importance of on-treatment mean and visit-to-visit blood pressure variability in ONTARGET and TRANSCEND patients. *Hypertension* 2017;70:938–948.
  242. Parati G, Ochoa JE, Bilo G, Zanchetti A. SPRINT blood pressure: Sprinting back to Smirk's basal blood pressure? *Hypertension* 2017;69:15–19.
  243. Mancia G, Parati G, Bilo G, Gao P, Fagard R, Redon J et al. Ambulatory blood pressure values in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET). *Hypertension* 2012;60:1400–1406.

244. Odden MC, McClure LA, Sawaya BP, White CL, Peralta CA, Field TS et al. Achieved blood pressure and outcomes in the Secondary Prevention of Small Subcortical Strokes Trial. *Hypertension* 2016;67:63–69.
245. Stevens VJ, Obarzanek E, Cook NR, Lee IM, Appel LJ, Smith West D et al. Trials for the Hypertension Prevention Research G. Long-term weight loss and changes in blood pressure: Results of the Trials of Hypertension Prevention, phase II. *Ann Intern Med* 2001;134:1–11.
246. Whelton PK, Appel LJ, Espeland MA, Applegate WB, Ettinger WH Jr, Kostis JB et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: A randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. *JAMA* 1998;279:839–846.
247. Elliott P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, Marmot M. Intersalt revisited: Further analyses of 24 h sodium excretion and blood pressure within and across populations. Intersalt Cooperative Research Group. *BMJ* 1996;312:1249–1253.
248. He FJ, Li J, Macgregor GA. Effect of longer-term modest salt reduction on blood pressure. *Cochrane Database Syst Rev* 2013;4:CD004937.
249. Suckling RJ, He FJ, Markandu ND, MacGregor GA. Modest salt reduction lowers blood pressure and albumin excretion in impaired glucose tolerance and type 2 diabetes mellitus: A randomized doubleblind trial. *Hypertension* 2016;67:1189–1195.
250. Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of low-sodium diet vs. high-sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride (Cochrane Review). *Am J Hypertens* 2012;25:1–15.
251. He FJ, MacGregor GA. How far should salt intake be reduced? *Hypertension* 2003;42:1093–1099.
252. Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ, Goldman L. Projected effect of dietary salt reductions on future cardiovascular disease. *N Engl J Med* 2010;362:590–599.
253. He FJ, Burnier M, Macgregor GA. Nutrition in cardiovascular disease: Salt in hypertension and heart failure. *Eur Heart J* 2011;32:3073–3080.
254. He FJ, MacGregor GA. Salt reduction lowers cardiovascular risk: Metaanalysis of outcome trials. *Lancet* 2011;378:380–382.
255. Taylor RS, Ashton KE, Moxham T, Hooper L, Ebrahim S. Reduced dietary salt for the prevention of cardiovascular disease: A meta-analysis of randomized controlled trials (Cochrane review). *Am J Hypertens* 2011;24:843–853.
256. Mente A, O'Donnell M, Rangarajan S, Dagenais G, Lear S, McQueen M et al. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: A pooled analysis of data from four studies. *Lancet* 2016;388:465–475.
257. Binia A, Jaeger J, Hu Y, Singh A, Zimmermann D. Daily potassium intake and sodium-to-potassium ratio in the reduction of blood pressure: A meta-analysis of randomized controlled trials. *J Hypertens* 2015;33:1509–1520.
258. Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ. Effect of lower sodium intake on health: Systematic review and meta-analyses. *BMJ* 2013;346:f1326.
259. O'Donnell M, Mente A, Rangarajan S, McQueen MJ, Wang X, Liu L et al. PURE Investigators. Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N Engl J Med* 2014;371:612–623.
260. Cushman WC, Cutler JA, Hanna E, Bingham SF, Follmann D, Harford T et al. Prevention and Treatment of Hypertension Study (PATHS): Effects of an alcohol treatment program on blood pressure. *Arch Intern Med* 1998;158:1197–1207.
261. Holmes MV, Dale CE, Zuccolo L, Silverwood RJ, Guo Y, Ye Z et al. InterAct Consortium. Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. *BMJ* 2014;349:g4164.
262. Dickinson HO, Mason JM, Nicolson DJ, Campbell F, Beyer FR, Cook JV et al. Lifestyle interventions to reduce raised blood pressure: A systematic review of randomized controlled trials. *J Hypertens* 2006;24:215–233.
263. Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med* 2009;169:659–669.
264. Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: An updated systematic review and meta-analysis. *Am J Clin Nutr* 2010;92:1189–1196.
265. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F et al. PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;368:1279–1290.
266. Domenech M, Roman P, Lapetra J, Garcia de la Corte FJ, Sala-Vila A, de la Torre R et al. Mediterranean diet reduces 24-h ambulatory blood pressure, blood glucose, and lipids: One-year randomized, clinical trial. *Hypertension* 2014;64:69–76.
267. Ding M, Bhupathiraju SN, Satija A, van Dam RM, Hu FB. Long-term coffee consumption and risk of cardiovascular disease: A systematic review and a dose-response meta-analysis of prospective cohort studies. *Circulation* 2014;129:643–659.
268. Li G, Zhang Y, Thabane L, Mbuagbaw L, Liu A, Levine MA. Holbrook Effect of green tea supplementation on blood pressure among overweight and obese adults: A systematic review and meta-analysis. *J Hypertens* 2015;33:243–254.
269. Greyling A, Ras RT, Zock PL, Lorenz M, Hopman MT, Thijssen DH, Draijer R. The effect of black tea on blood pressure: A systematic review with meta-analysis of randomized controlled trials. *PLOS ONE* 2014;9:e103247.
270. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: Interaction of neurohumoral and renal mechanisms. *Circ Res* 2015;116:991–1006.
271. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure: A meta-analysis of randomized controlled trials. *Hypertension* 2003;42:878–884.
272. Prospective Studies Collaboration Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J et al. Body-mass index and causespecific mortality in 900,000 adults: Collaborative analyses of 57 prospective studies. *Lancet* 2009;373:1083–1096.
273. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: A systematic review and meta-analysis. *JAMA* 2013;309:71–82.
274. Global BMI Mortality Collaboration Di Angelantonio E, Bhupathiraju Sh N, Wormser D, Gao P, Kaptoge S, Berrington de Gonzalez A et al. Body-mass index and all-cause mortality: Individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet* 2016;388:776–786.
275. Jebb SA, Ahern AL, Olson AD, Aston LM, Holzapfel C, Stoll J et al. Primary care referral to a commercial provider for weight loss treatment versus standard care: A randomised controlled trial. *Lancet* 2011;378:1485–1492.
276. Jordan J, Yumuk V, Schlaich M, Nilsson PM, Zahorska-Markiewicz B, Grassi G et al. Joint statement of the European Association for the Study of Obesity and the European Society of Hypertension: Obesity and difficult to treat arterial hypertension. *J Hypertens* 2012;30:1047–1055.
277. Cornelissen VA, Smart NA. Exercise training for blood pressure: A systematic review and meta-analysis. *J Am Heart Assoc* 2013;2:e004473.
278. Leitzmann MF, Park Y, Blair A, Ballard-Barbash R, Mouw T, Hollenbeck AR, Schatzkin A. Physical activity recommendations and decreased risk of mortality. *Arch Intern Med* 2007;167:2453–2460.
279. Rossi A, Dikareva A, Bacon SL, Daskalopoulou SS. The impact of physical activity on mortality in patients with high blood pressure: A systematic review. *J Hypertens* 2012;30:1277–1288.
280. Mann SJ, James GD, Wang RS, Pickering TG. Elevation of ambulatory systolic blood pressure in hypertensive smokers. A case-control study. *JAMA* 1991;265:2226–2228.
281. Kotseva K, Wood D, De Bacquer D, De Backer G, Ryden L, Jennings C et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol* 2016;23:636–648.
282. Yarlioglu M, Kaya MG, Ardic I, Calapkorur B, Dogdu O, Akpek M et al. Acute effects of passive smoking on blood pressure and heart rate in healthy females. *Blood Press Monit* 2010;15:251–256.
283. Groppelli A, Giorgi DM, Omboni S, Parati G, Mancia G. Persistent blood pressure increase induced by heavy smoking. *J Hypertens* 1992;10:495–499.
284. Primatesta P, Falaschetti E, Gupta S, Marmot MG, Poulter NR. Association between smoking and blood pressure: Evidence from the health survey for England. *Hypertension* 2001;37:187–193.
285. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. *BMJ* 1994;309:901–911.
286. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H et al. A comparative risk assessment of burden of disease and



- injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2224–2260.
287. Stead LF, Buitrago D, Preciado N, Sanchez G, Hartmann-Boyce J, Lancaster T. Physician advice for smoking cessation. *Cochrane Database Syst Rev* 2013;5:CD000165.
  288. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: An overview and network meta-analysis. *Cochrane Database Syst Rev* 2013;5:CD009329.
  289. Stead LF, Koilpillai P, Fanshawe TR, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev* 2016;3:CD008286.
  290. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med* 2010;363:2211–2219.
  291. Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD et al. ALTITUDE Investigators. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012;367:2204–2213.
  292. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure-lowering on outcome incidence in hypertension: 5. Head-to-head comparisons of various classes of antihypertensive drugs – overview and meta-analyses. *J Hypertens* 2015;33:1321–1341.
  293. Corrao G, Zambon A, Parodi A, Poluzzi E, Baldi I, Merlino L et al. Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: A population-based study in Italy. *J Hypertens* 2008;26:819–824.
  294. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment in hypertension: 9. Discontinuations for adverse events attributed to different classes of antihypertensive drugs: Metaanalyses of randomized trials. *J Hypertens* 2016;34:1921–1932.
  295. Volpe M, Mancia G, Trimarco B. Angiotensin II receptor blockers and myocardial infarction: Deeds and misdeeds. *J Hypertens* 2005;23:2113–2118.
  296. Reboldi G, Angeli F, Cavallini C, Gentile G, Mancia G, Verdecchia P. Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of myocardial infarction, stroke and death: A meta-analysis. *J Hypertens* 2008;26:1282–1289.
  297. Kronish IM, Woodward M, Sergie Z, Ogedegbe G, Falzon L, Mann DM. Meta-analysis: Impact of drug class on adherence to antihypertensives. *Circulation* 2011;123:1611–1621.
  298. Fried LF, Emanuele N, Zhang JH, Brophy M, Conner TA, Duckworth W et al. VA NEPHRON-D Investigators. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;369:1892–1903.
  299. ONTARGET Investigators Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547–1559.
  300. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 4. Effects of various classes of antihypertensive drugs – overview and meta-analyses. *J Hypertens* 2015;33:195–211.
  301. Roush GC, Ernst ME, Kostis JB, Tandon S, Sica DA. Head-to-head comparisons of hydrochlorothiazide with indapamide and chlorthalidone: Antihypertensive and metabolic effects. *Hypertension* 2015;65:1041–1046.
  302. Olde Engberink RH, Frenkel WJ, van den Bogaard B, Brewster LM, Vogt L, van den Born BJ. Effects of thiazide-type and thiazide-like diuretics on cardiovascular events and mortality: Systematic review and meta-analysis. *Hypertension* 2015;65:1033–1040.
  303. Zanchetti A, Mancia G. Strategies for antihypertensive treatment decisions: How to assess benefits? *J Hypertens* 1997;15:215–216.
  304. Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL. Thiazide diuretics, potassium, and the development of diabetes: A quantitative review. *Hypertension* 2006;48:219–224.
  305. Brown MJ, Williams B, Morant SV, Webb DJ, Caulfield MJ, Cruickshank JK et al. Effect of amiloride, or amiloride plus hydrochlorothiazide, versus hydrochlorothiazide on glucose tolerance and blood pressure (PATHWAY-3): A parallel-group, double-blind randomised phase 4 trial. *Lancet Diabetes Endocrinol* 2016;4:136–147.
  306. Dondo TB, Hall M, West RM, Jernberg T, Lindahl B, Bueno H et al. Beta-blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. *J Am Coll Cardiol* 2017;69:2710–2720.
  307. Bakris GL, Fonseca V, Katholi RE, McGill JB, Messerli FH, Phillips RA et al. GEMINI Investigators. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: A randomized controlled trial. *JAMA* 2004;292:2227–2236.
  308. Ayers K, Byrne LM, DeMatteo A, Brown NJ. Differential effects of nebivolol and metoprolol on insulin sensitivity and plasminogen activator inhibitor in the metabolic syndrome. *Hypertension* 2012;59:893–898.
  309. Chapman N, Chang CL, Dahlof B, Sever PS, Wedel H, Poulter NR. Effect of doxazosin gastrointestinal therapeutic system as third-line antihypertensive therapy on blood pressure and lipids in the AngloScandinavian Cardiac Outcomes Trial. *Circulation* 2008;118:42–48.
  310. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G et al. British Hypertension Society's PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): A randomised, double-blind, crossover trial. *Lancet* 2015;386:2059–2068.
  311. Wang YR, Alexander GC, Stafford RS. Outpatient hypertension treatment, treatment intensification, and control in Western Europe and the United States. *Arch Intern Med* 2007;167:141–147.
  312. Corrao G, Parodi A, Nicotra F, Zambon A, Merlino L, Cesana G, Mancia G. Better compliance to antihypertensive medications reduces cardiovascular risk. *J Hypertens* 2011;29:610–618.
  313. Tiffe T, Wagner M, Rucker V, Morbach C, Gelbrich G, Stork S, Heuschmann PU. Control of cardiovascular risk factors and its determinants in the general population – findings from the STAAB cohort study. *BMC Cardiovasc Disord* 2017;17:276.
  314. Mensah GA, Bakris G. Treatment and control of high blood pressure in adults. *Cardiol Clin* 2010;28:609–622.
  315. Gupta P, Patel P, Strauch B, Lai FY, Akbarov A, Gulsin GS et al. Biochemical screening for nonadherence is associated with blood pressure reduction and improvement in adherence. *Hypertension* 2017;70:1042–1048.
  316. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981–2997.
  317. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U et al. LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): A randomised trial against atenolol. *Lancet* 2002;359:995–1003.
  318. Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M et al. ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): A multicentre randomised controlled trial. *Lancet* 2005;366:895–906.
  319. McKavanagh P, Lusk L, Ball PA, Verghis RM, Agus AM, Trinick TR et al. A comparison of cardiac computerized tomography and exercise stress electrocardiogram test for the investigation of stable chest pain: The clinical results of the CAPP randomized prospective trial. *Eur Heart J Cardiovasc Imaging* 2015;16:441–448.
  320. Hedner T. Progress report on the Nordic diltiazem study (NORDIL): An outcome study in hypertensive patients. *Blood Press* 1999;8:296–299.
  321. Elgendy IY, Bavry AA, Gong Y, Handberg EM, Cooper-DeHoff RM, Pepine CJ. Long-term mortality in hypertensive patients with coronary artery disease: Results from the US cohort of the International Verapamil (SR)/Trandolapril Study. *Hypertension* 2016;68:1110–1114.
  322. Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. *Br Med J (Clin Res Ed)* 1986;293:1145–1151.
  323. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991;265:3255–3264.
  324. Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 1991;338:1281–1285.
  325. Mancia G, Grassi G, Zanchetti A. New-onset diabetes and antihypertensive drugs. *J Hypertens* 2006;24:3–10.
  326. Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T, Ruilope LM. Morbidity and mortality in patients

- randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 2000;356:366–372.
327. Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V et al. ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008;359:2417–2428.
  328. Ogiwara T, Saruta T, Rakugi H, Saito I, Shimamoto K, Matsuoka H et al. COLM Investigators. Combination therapy of hypertension in the elderly: A subgroup analysis of the Combination of OLMesartan and a calcium channel blocker or diuretic in Japanese elderly hypertensive patients trial. *Hypertens Res* 2015;38:89–96.
  329. Matsuzaki M, Ogiwara T, Umemoto S, Rakugi H, Matsuoka H, Shimada K et al. Combination Therapy of Hypertension to Prevent Cardiovascular Events Trial Group. Prevention of cardiovascular events with calcium channel blocker-based combination therapies in patients with hypertension: A randomized controlled trial. *J Hypertens* 2011;29:1649–1659.
  330. Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, Group SS et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): Principal results of a randomized double-blind intervention trial. *J Hypertens* 2003;21:875–886.
  331. Liu L, Zhang Y, Liu G, Li W, Zhang X, Zanchetti A, Group FS. The Felodipine Event Reduction (FEVER) Study: A randomized long-term placebo-controlled trial in Chinese hypertensive patients. *J Hypertens* 2005;23:2157–2172.
  332. Staessen JA, Fagard R, Thijs L, Celis H, Arabadzisz GG, Birkenhager WH et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 1997;350:757–764.
  333. Wang JG, Staessen JA, Gong L, Liu L. Chinese trial on isolated systolic hypertension in the elderly. Systolic Hypertension in China (SystChina) Collaborative Group. *Arch Intern Med* 2000;160:211–220.
  334. Hansson L, Lindholm LH, Ekblom T, Dahlöf B, Lanke J, Schersten B et al. Randomised trial of old and new antihypertensive drugs in elderly patients: Cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999;354:1751–1756.
  335. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: The Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999;353:611–616.
  336. Zanchetti A, Hennig M, Baurecht H, Tang R, Cuspidi C, Carugo S, Mancia G. Prevalence and incidence of the metabolic syndrome in the European Lacidipine Study on Atherosclerosis (ELSA) and its relation with carotid intima-media thickness. *J Hypertens* 2007;25:2463–2470.
  337. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L et al. VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: The VALUE randomised trial. *Lancet* 2004;363:2022–2031.
  338. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;358:1033–1041.
  339. Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: The Nordic Diltiazem (NORDIL) study. *Lancet* 2000;356:359–365.
  340. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH et al. Investigators I. A calcium antagonist vs a noncalcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): A randomized controlled trial. *JAMA* 2003;290:2805–2816.
  341. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ Combination therapy versus monotherapy in reducing blood pressure: Meta-analysis on 11,000 participants from 42 trials. *Am J Med* 2009;122:290–300.
  342. MacDonald TM, Williams B, Webb DJ, Morant S, Caulfield M, Cruickshank JK et al. British Hypertension Society Programme of Prevention And Treatment of Hypertension With Algorithm-based Therapy (PATHWAY). Combination therapy is superior to sequential monotherapy for the initial treatment of hypertension: A double-blind randomized controlled trial. *J Am Heart Assoc* 2017;6:e006986.
  343. Yusuf S, Lonn E, Pais P, Bosch J, Lopez-Jaramillo P, Zhu J et al. HOPE-3 Investigators. Blood-pressure and cholesterol lowering in persons without cardiovascular disease. *N Engl J Med* 2016;374:2032–2043.
  344. Xu W, Goldberg SI, Shubina M, Turchin A. Optimal systolic blood pressure target, time to intensification, and time to follow-up in treatment of hypertension: Population based retrospective cohort study. *BMJ* 2015;350:h158.
  345. Egan BM, Bandyopadhyay D, Shaftman SR, Wagner CS, Zhao Y, Yulsensberg KS. Initial monotherapy and combination therapy and hypertension control the first year. *Hypertension* 2012;59:1124–1131.
  346. Corrao G, Parodi A, Zambon A, Heiman F, Filippi A, Cricelli C et al. Reduced discontinuation of antihypertensive treatment by two-drug combination as first step. Evidence from daily life practice. *J Hypertens* 2010;28:1584–1590.
  347. Conn VS, Ruppar TM, Chase JA, Enriquez M, Cooper PS. Interventions to improve medication adherence in hypertensive patients: Systematic review and meta-analysis. *Curr Hypertens Rep* 2015;17:94.
  348. Mancia G, Rea F, Cuspidi C, Grassi G, Corrao G. Blood pressure control in hypertension. Pros and cons of available treatment strategies. *J Hypertens* 2017;35:225–233.
  349. Weir MR, Hsueh WA, Nesbitt SD, Littlejohn TJ III, Graff A, Shojaae A et al. A titrate-to-goal study of switching patients uncontrolled on antihypertensive monotherapy to fixed-dose combinations of amlodipine and olmesartan medoxomil ± hydrochlorothiazide. *J Clin Hypertens (Greenwich)* 2011;13:404–412.
  350. Volpe M, Christian Rump L, Ammentorp B, Laeis P. Efficacy and safety of triple antihypertensive therapy with the olmesartan/amlodipine/ hydrochlorothiazide combination. *Clin Drug Investig* 2012;32:649–664.
  351. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: A metaanalysis. *Hypertension* 2010;55:399–407.
  352. Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, Toennes SW. Resistant hypertension? Assessment of adherence by toxicological urine analysis. *J Hypertens* 2013;31:766–774.
  353. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;39:119–177.
  354. Gupta P, Patel P, Horne R, Buchanan H, Williams B, Tomaszewski M. How to screen for nonadherence to antihypertensive therapy. *Curr Hypertens Rep* 2016;18:89.
  355. Coca A, Agabiti Rosei E, Cifkova R, Manolis AJ, Redon J, Mancia G. The polypill in cardiovascular prevention: Evidence, limitations and perspective – position paper of the European Society of Hypertension. *J Hypertens* 2017;35:1546–1553.
  356. Castellano JM, Sanz G, Penalvo JL, Bansilal S, Fernandez-Ortiz A, Alvarez L et al. A polypill strategy to improve adherence: Results from the FOCUS project. *J Am Coll Cardiol* 2014;64:2071–2082.
  357. Williams B, MacDonald TM, Morant SV, Webb DJ, Sever P, McInnes GT et al. British Hypertension Society programme of Prevention And Treatment of Hypertension with Algorithm based Therapy (PATHWAY) Study Group. Endocrine and haemodynamic changes in resistant hypertension, and blood pressure responses to spironolactone or amiloride: The PATHWAY-2 mechanisms substudies. *Lancet Diabetes Endocrinol* 2018;6:464–475.
  358. Bisognano JD, Bakris G, Nadim MK, Sanchez L, Kroon AA, Schafer J et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: Results from the double-blind, randomized, placebo-controlled rheos pivotal trial. *J Am Coll Cardiol* 2011;58:765–773.
  359. Wachter R, Halbach M, Bakris GL, Bisognano JD, Haller H, Beige J et al. An exploratory propensity score matched comparison of second-generation and first-generation baroreflex activation therapy systems. *J Am Soc Hypertens* 2017;11:81–91.
  360. Spiering W, Williams B, Van der Heyden J, van Kleef M, Lo R, Versmissen J et al. CALM-FIM\_EUR Investigators. Endovascular baroreflex amplification for resistant hypertension: A safety and proof-of-principle clinical study. *Lancet* 2017;390:2655–2661.



361. DiBona GF. Physiology in perspective: The wisdom of the body. *Neural control of the kidney. Am J Physiol Regul Integr Comp Physiol* 2005;289:R633–R641.
362. Esler M. Sympathetic nervous system moves toward center stage in cardiovascular medicine: From Thomas Willis to resistant hypertension. *Hypertension* 2014;63:e25–e32.
363. Mahfoud F, Bohm M, Azizi M, Pathak A, Durand Zaleski I, Ewen S et al. Proceedings from the European Clinical Consensus Conference for Renal Denervation: Considerations on future clinical trial design. *Eur Heart J* 2015;36:2219–2227.
364. Bohm M, Mahfoud F, Ukena C, Hoppe UC, Narkiewicz K, Negoita M et al. GSR Investigators. First report of the Global SYMPPLICITY Registry on the effect of renal artery denervation in patients with uncontrolled hypertension. *Hypertension* 2015;65:766–774.
365. Krum H, Schlaich MP, Sobotka PA, Bohm M, Mahfoud F, Rocha-Singh K et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: Final 3-year report of the Symplicity HTN-1 study. *Lancet* 2014;383:622–629.
366. Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA et al., Spyral HTN-OFF Med trial investigators. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): A randomised, sham-controlled, proof-of-concept trial. *Lancet* 2017;390:2160–2170.
367. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT et al., for the Symplicity HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014;370:1393–1401.
368. Mathiassen ON, Vase H, Bech JN, Christensen KL, Buus NH, Schroeder AP et al. Renal denervation in treatment-resistant essential hypertension. A randomized, SHAM-controlled, double-blinded 24-h blood pressure-based trial. *J Hypertens* 2016;34:1639–1647.
369. Azizi M, Sapoval M, Gosse P, Monge M, Bobrie G, Delsart P et al., DENERHTN Investigators. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): A multicentre, open-label, randomised controlled trial. *Lancet* 2015;385:1957–1965.
370. Rosa J, Widimsky P, Tousek P, Petrak O, Curila K, Waldauf P et al. Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: Six-month results from the Prague-15 study. *Hypertension* 2015;65:407–413.
371. Mahfoud F, Schmieder RE, Azizi M, Pathak A, Sievert H, Tsioufiss C et al. Proceedings from the 2nd European Clinical Consensus Conference for device-based therapies for hypertension: State of the art and considerations for the future. *Eur Heart J* 2017;38:3272–3281.
372. Ewen S, Ukena C, Linz D, Kindermann I, Cremers B, Laufs U et al. Reduced effect of percutaneous renal denervation on blood pressure in patients with isolated systolic hypertension. *Hypertension* 2015;65:193–199.
373. Mahfoud F, Bakris G, Bhatt DL, Esler M, Ewen S, Fahy M et al. Reduced blood pressure-lowering effect of catheter-based renal denervation in patients with isolated systolic hypertension: Data from SYMPPLICITY HTN-3 and the Global SYMPPLICITY Registry. *Eur Heart J* 2017;38:93–100.
374. Burchell AE, Lobo MD, Sulke N, Sobotka PA, Paton JF. Arteriovenous anastomosis: Is this the way to control hypertension? *Hypertension* 2014;64:6–12.
375. Ng FL, Saxena M, Mahfoud F, Pathak A, Lobo MD. Device-based therapy for hypertension. *Curr Hypertens Rep* 2016;18:61.
376. Faul J, Schoors D, Brouwers S, Scott B, Jerrentrup A, Galvin J et al. Creation of an iliac arteriovenous shunt lowers blood pressure in chronic obstructive pulmonary disease patients with hypertension. *J Vasc Surg* 2014;59:1078–1083.
377. Lobo MD, Sobotka PA, Stanton A, Cockcroft JR, Sulke N, Dolan E et al., ROX CONTROL HTN Investigators. Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): A randomised controlled trial. *Lancet* 2015;385:1634–1641.
378. Ott C, Lobo MD, Sobotka PA, Mahfoud F, Stanton A, Cockcroft J et al. Effect of arteriovenous anastomosis on blood pressure reduction in patients with isolated systolic hypertension compared with combined hypertension. *J Am Heart Assoc* 2016;5:e004234.
379. McBryde FD, Abdala AP, Hendy EB, Pijacka W, Marvar P, Moraes DJ et al. The carotid body as a putative therapeutic target for the treatment of neurogenic hypertension. *Nat Commun* 2013;4:2395.
380. Narkiewicz K, Ratcliffe LE, Hart EC, Briant LJ, Chrostowska M, Wolf J et al. Unilateral carotid body resection in resistant hypertension: A safety and feasibility trial. *JACC Basic Transl Sci* 2016;1:313–324.
381. Niewinski P, Janczak D, Rucinski A, Tubek S, Engelman ZJ, Piesiak P et al. Carotid body resection for sympathetic modulation in systolic heart failure: Results from first-in-man study. *Eur J Heart Fail* 2017;19:391–400.
382. Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL et al. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation* 2012;125:1635–1642.
383. Myat A, Redwood SR, Qureshi AC, Spertus JA, Williams B. Resistant hypertension. *BMJ* 2012;345:e7473.
384. de la Sierra A, Banegas JR, Segura J, Gorostidi M, Ruilope LM. Ambulatory blood pressure monitoring and development of cardiovascular events in high-risk patients included in the Spanish ABPM registry: The CARDIORISC Event study. *J Hypertens* 2012;30:713–719.
385. Williams B. Resistant hypertension: An unmet treatment need. *Lancet* 2009;374:1396–1398.
386. Mantero F, Mattarello MJ, Albiger NM. Detecting and treating primary aldosteronism: Primary aldosteronism. *Exp Clin Endocrinol Diabetes* 2007;115:171–174.
387. Fagard RH. Resistant hypertension. *Heart* 2012;98:254–261.
388. Laurent S, Schlaich M, Esler M. New drugs, procedures, and devices for hypertension. *Lancet* 2012;380:591–600.
389. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: Longitudinal study of electronically compiled dosing histories. *BMJ* 2008;336:1114–1117.
390. Bakris GL, Lindholm LH, Black HR, Krum H, Linas S, Linseman JV et al. Divergent results using clinic and ambulatory blood pressures: Report of a darusentan-resistant hypertension trial. *Hypertension* 2010;56:824–830.
391. Oxlund CS, Henriksen JE, Tarnow L, Schousboe K, Gram J, Jacobsen IA. Low dose spironolactone reduces blood pressure in patients with resistant hypertension and type 2 diabetes mellitus: A double blind randomized clinical trial. *J Hypertens* 2013;31:2094–2102.
392. Liu L, Xu B, Ju Y. Addition of spironolactone in patients with resistant hypertension: A meta-analysis of randomized controlled trials. *Clin Exp Hypertens* 2017;39:257–263.
393. Zhao D, Liu H, Dong P, Zhao J. A meta-analysis of add-on use of spironolactone in patients with resistant hypertension. *Int J Cardiol* 2017;233:113–117.
394. Wang C, Xiong B, Huang J. Efficacy and safety of spironolactone in patients with resistant hypertension: A meta-analysis of randomised controlled trials. *Heart Lung Circ* 2016;25:1021–1030.
395. Pimenta E, Gaddam KK, Oparil S, Aban I, Husain S, Dell'Italia LJ, Calhoun DA. Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: Results from a randomized trial. *Hypertension* 2009;54:475–481.
396. Rimoldi SF, Scherrer U, Messerli FH. Secondary arterial hypertension: When, who, and how to screen? *Eur Heart J* 2014;35:1245–1254.
397. Grossman A, Messerli FH, Grossman E. Drug induced hypertension. An unappreciated cause of secondary hypertension. *Eur J Pharmacol* 2015;763:15–22.
398. van den Born BJ et al. ESC Council on hypertension position document on the management of hypertensive emergencies. *Eur Heart J Cardiovasc Pharmacother* 2018;Aug 25. doi: [10.1093/ehjcvp/pyy032](https://doi.org/10.1093/ehjcvp/pyy032). [Epub ahead of print].
399. Vaughan CJ, Delanty N. Hypertensive emergencies. *Lancet* 2000;356:411–417.
400. Chester EM, Agamanolis DP, Banker BQ, Victor M. Hypertensive encephalopathy: A clinicopathologic study of 20 cases. *Neurology* 1978;28:928–939.
401. van den Born BJ, Koopmans RP, Groeneveld JO, van Montfrans GA. Ethnic disparities in the incidence, presentation and complications of malignant hypertension. *J Hypertens* 2006;24:2299–2304.
402. Cremer A, Amraoui F, Lip GY, Morales E, Rubin S, Segura J et al. From malignant hypertension to hypertension-MOD: A modern definition for an old but still dangerous emergency. *J Hum Hypertens* 2016;30:463–466.
403. Pinna G, Pascale C, Fornengo P, Arras S, Piras C, Panzarasa P et al. Hospital admissions for hypertensive crisis in the emergency departments: A large multicenter Italian study. *PLOS ONE* 2014;9:e93542.
404. van den Born BJ, Lowenberg EC, van der Hoeven NV, de Laat B, Meijers JC, Levi M, van Montfrans GA. Endothelial dysfunction,

- platelet activation, thrombogenesis and fibrinolysis in patients with hypertensive crisis. *J Hypertens* 2011;29:922–927.
405. Grassi D, O'Flaherty M, Pellizzari M, Bendersky M, Rodriguez P, Turri D et al. Hypertensive urgencies in the emergency department: Evaluating blood pressure response to rest and to antihypertensive drugs with different profiles. *J Clin Hypertens (Greenwich)* 2008;10:662–667.
  406. Perez MI, Musini VM. Pharmacological interventions for hypertensive emergencies: A Cochrane systematic review. *J Hum Hypertens* 2008;22:596–607.
  407. Lane DA, Lip GY, Beevers DG. Improving survival of malignant hypertension patients over 40 years. *Am J Hypertens* 2009;22:1199–1204.
  408. Amraoui F, Van Der Hoeven NV, Van Valkengoed IG, Vogt L, Van Den Born BJ. Mortality and cardiovascular risk in patients with a history of malignant hypertension: A case-control study. *J Clin Hypertens (Greenwich)* 2014;16:122–126.
  409. Gonzalez R, Morales E, Segura J, Ruilope LM, Praga M. Long-term renal survival in malignant hypertension. *Nephrol Dial Transplant* 2010;25:3266–3272.
  410. Cuspidi C, Rescaldani M, Tadic M, Sala C, Grassi G, Mancia G. Whitecoat hypertension, as defined by ambulatory blood pressure monitoring, and subclinical cardiac organ damage: A meta-analysis. *J Hypertens* 2015;33:24–32.
  411. Mancia G, Bombelli M, Facchetti R, Madotto F, Quarti-Trevano F, Grassi G, Segura R. Increased long-term risk of new-onset diabetes mellitus in white-coat and masked hypertension. *J Hypertens* 2009;27:1672–1678.
  412. Tientcheu D, Ayers C, Das SR, McGuire DK, de Lemos JA, Khera A et al. Target organ complications and cardiovascular events associated with masked hypertension and white-coat hypertension: Analysis from the Dallas Heart Study. *J Am Coll Cardiol* 2015;66:2159–2169.
  413. Fagard RH, Staessen JA, Thijs L, Gasowski J, Bulpitt CJ, Clement D et al. Response to antihypertensive therapy in older patients with sustained and nonsustained systolic hypertension. Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Circulation* 2000;102:1139–1144.
  414. Mancia G, Facchetti R, Parati G, Zanchetti A. Effect of long-term antihypertensive treatment on white-coat hypertension. *Hypertension* 2014;64:1388–1398.
  415. Staessen JA, Celis H, Thijs L, Fagard R, Amery AK. Efficacy of antihypertensive drugs given once a day: The calcium antagonists revisited. *J Hypertens Suppl* 1994;12:S107–S115.
  416. Bulpitt CJ, Beckett NS, Peters R, Leonetti G, Gergova V, Fagard R et al. Blood pressure control in the Hypertension in the Very Elderly Trial (HYVET). *J Hum Hypertens* 2012;26:157–163.
  417. Franklin SS, Thijs L, Asayama K, Li Y, Hansen TW, Boggia J et al., IDACO Investigators. The cardiovascular risk of white-coat hypertension. *J Am Coll Cardiol* 2016;68:2033–2043.
  418. Franklin SS, Thijs L, Hansen TW, Li Y, Boggia J, Kikuya M et al., International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes Investigators. Significance of white-coat hypertension in older persons with isolated systolic hypertension: A meta-analysis using the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes population. *Hypertension* 2012;59:564–571.
  419. Mancia G, Bombelli M, Brambilla G, Facchetti R, Segura R, Toso E, Grassi G. Long-term prognostic value of white coat hypertension: An insight from diagnostic use of both ambulatory and home blood pressure measurements. *Hypertension* 2013;62:168–174.
  420. Mancia G, Facchetti R, Grassi G, Bombelli M. Adverse prognostic value of persistent office blood pressure elevation in white coat hypertension. *Hypertension* 2015;66:437–444.
  421. Gorostidi M, Banegas JR, de la Sierra A, Vinyoles E, Segura J, Ruilope LM. Ambulatory blood pressure monitoring in daily clinical practice – the Spanish ABPM Registry experience. *Eur J Clin Invest* 2016;46:92–98.
  422. Mancia G, Bombelli M, Facchetti R, Madotto F, Quarti-Trevano F, Polo Friz H et al. Long-term risk of sustained hypertension in white-coat or masked hypertension. *Hypertension* 2009;54:226–232.
  423. Ogedegbe G, Agyemang C, Ravenell JE. Masked hypertension: Evidence of the need to treat. *Curr Hypertens Rep* 2010;12:349–355.
  424. Sundstrom J, Neovius M, Tynelius P, Rasmussen F. Association of blood pressure in late adolescence with subsequent mortality: Cohort study of Swedish male conscripts. *BMJ* 2011;342:d643.
  425. Zanchetti A, Thomopoulos C, Parati G. Randomized controlled trials of blood pressure lowering in hypertension: A critical reappraisal. *Circ Res* 2015;116:1058–1073.
  426. Williams B. High blood pressure in young people and premature death. *BMJ* 2011;342:d1104.
  427. Julius S, Nesbitt SD, Egan BM, Weber MA, Michelson EL, Kaciroti N et al., Trial of Preventing Hypertension Study Investigators. Feasibility of treating prehypertension with an angiotensin-receptor blocker. *N Engl J Med* 2006;354:1685–1697.
  428. O'Rourke MF, Adji A. Guidelines on guidelines: Focus on isolated systolic hypertension in youth. *J Hypertens* 2013;31:649–654.
  429. Yano Y, Stamler J, Garside DB, Daviglus ML, Franklin SS, Carnethon MR et al. Isolated systolic hypertension in young and middle-aged adults and 31-year risk for cardiovascular mortality: The Chicago Heart Association Detection Project in Industry study. *J Am Coll Cardiol* 2015;65:327–335.
  430. Palatini P, Mormino P, Canali C, Santonastaso M, De Venuto G, Zanata G, Pessina AC. Factors affecting ambulatory blood pressure reproducibility. Results of the HARVEST Trial. Hypertension and Ambulatory Recording Venetia Study. *Hypertension* 1994;23:211–216.
  431. Briassoulis A, Agarwal V, Tousoulis D, Stefanadis C. Effects of antihypertensive treatment in patients over 65 years of age: A meta-analysis of randomised controlled studies. *Heart* 2014;100:317–323.
  432. Corrao G, Rea F, Monzio Compagnoni M, Merlino L, Mancia G. Protective effects of antihypertensive treatment in patients aged 85 years or older. *J Hypertens* 2017;35:1432–1441.
  433. Corrao G, Mazzola P, Monzio Compagnoni M, Rea F, Merlino L, Annoni G, Mancia G. Antihypertensive medications, loop diuretics, and risk of hip fracture in the elderly: A population-based cohort study of 81,617 Italian patients newly treated between 2005 and 2009. *Drugs Aging* 2015;32:927–936.
  434. Kjeldsen SE, Steneshjem A, Os I, Van de Borne P, Burnier M, Narkiewicz K et al. Treatment of high blood pressure in elderly and octogenarians: European Society of Hypertension statement on blood pressure targets. *Blood Press* 2016;25:333–336.
  435. ESC Committee for Practice Guidelines. Guidelines on the management of cardiovascular diseases during pregnancy 2018. *Eur Heart J* 2018; Aug 25. doi: 10.1093/eurheartj/ehy340. [Epub ahead of print].
  436. American College of Obstetricians Gynecologists Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 2013;122:1122–1131.
  437. Lowe SA, Bowyer L, Lust K, McMahon LP, Morton MR, North RA et al. The SOMANZ Guidelines for the management of hypertensive disorders of pregnancy 2014. *Aust N Z J Obstet Gynaecol* 2015;55:11–16.
  438. Bartsch E, Medcalf KE, Park AL, Ray JG. Clinical risk factors for preeclampsia determined in early pregnancy: Systematic review and meta-analysis of large cohort studies. *BMJ* 2016;353:i1753.
  439. Blood Pressure Association. Blood Pressure UK. <http://www.bloodpressureuk.org> (20 April 2018).
  440. Penny JA, Halligan AW, Shennan AH, Lambert PC, Jones DR, de Swiet M, Taylor DJ. Automated, ambulatory, or conventional blood pressure measurement in pregnancy: Which is the better predictor of severe hypertension? *Am J Obstet Gynecol* 1998;178:521–526.
  441. Schmella MJ, Clifton RG, Althouse AD, Roberts JM. Uric acid determination in gestational hypertension: Is it as effective a delineator of risk as proteinuria in high-risk women? *Reprod Sci* 2015;22:1212–1219.
  442. Chappell LC, Shennan AH. Assessment of proteinuria in pregnancy. *BMJ* 2008;336:968–969.
  443. Cnossen JS, Morris RK, ter Riet G, Mol BW, van der Post JA, Coomarasamy A et al. Use of uterine artery Doppler ultrasonography to predict preeclampsia and intrauterine growth restriction: A systematic review and bivariable meta-analysis. *CMAJ* 2008;178:701–711.
  444. Zeisler H, Lurba E, Chantraine F, Vathis M, Staff AC, Sennstrom M et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. *N Engl J Med* 2016;374:13–22.
  445. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med* 2017;377:613–622.
  446. Magee LA, von Dadelszen P, Singer J, Lee T, Rey E, Ross S et al., CHIPS Study Group. The CHIPS randomized controlled

- trial (Control of Hypertension in Pregnancy Study): Is severe hypertension just an elevated blood pressure? *Hypertension* 2016;68:1153–1159.
447. Redman CW. Fetal outcome in trial of antihypertensive treatment in pregnancy. *Lancet* 1976;2:753–756.
  448. Cockburn J, Moar VA, Ounsted M, Redman CW. Final report of study on hypertension during pregnancy: The effects of specific treatment on the growth and development of the children. *Lancet* 1982;1:647–649.
  449. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:3147–3197.
  450. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2014;2:CD002252.
  451. Magee LA, Cham C, Waterman EJ, Ohlsson A, von Dadelszen P. Hydralazine for treatment of severe hypertension in pregnancy: Meta-analysis. *BMJ* 2003;327:955–960.
  452. Duley L, Henderson-Smith DJ, Meher S. Drugs for treatment of very high blood pressure during pregnancy. *Cochrane Database Syst Rev* 2006;3:CD001449.
  453. Koopmans CM, Bijlenda D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ et al. Induction of labour versus expectant monitoring for gestational hypertension or mild preeclampsia after 36 weeks' gestation (HYPITAT): A multicentre, open-label randomised controlled trial. *Lancet* 2009;374:979–988.
  454. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): Population-based retrospective cohort study. *Lancet* 2005;366:1797–1803.
  455. Black MH, Zhou H, Sacks DA, Dublin S, Lawrence JM, Harrison TN, Reynolds K. Hypertensive disorders first identified in pregnancy increase risk for incident prehypertension and hypertension in the year after delivery. *J Hypertens* 2016;34:728–735.
  456. Chasan-Taber L, Willett WC, Manson JE, Spiegelman D, Hunter DJ, Curhan G et al. Prospective study of oral contraceptives and hypertension among women in the United States. *Circulation* 1996;94:483–489.
  457. Dong W, Colhoun HM, Poulter NR. Blood pressure in women using oral contraceptives: Results from the Health Survey for England 1994. *J Hypertens* 1997;15:1063–1068.
  458. Gillum LA, Mamidipudi SK, Johnston SC. Ischemic stroke risk with oral contraceptives: A meta-analysis. *JAMA* 2000;284:72–78.
  459. World Health Organization. *Medical eligibility criteria for contraceptive use*. Third ed. 2004. <http://apps.who.int/iris/bitstream/10665/42907/1/9241562668.pdf> (date accessed June 28th 2018).
  460. Lubianca JN, Moreira LB, Gus M, Fuchs FD. Stopping oral contraceptives: An effective blood pressure-lowering intervention in women with hypertension. *J Hum Hypertens* 2005;19:451–455.
  461. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women-2011 update: A guideline from the American Heart Association. *J Am Coll Cardiol* 2011;57:1404–1423.
  462. Issa Z, Seely EW, Rahme M, El-Hajj Fuleihan G. Effects of hormone therapy on blood pressure. *Menopause* 2015;22:456–468.
  463. Modesti PA, Reboldi G, Cappuccio FP, Agyemang C, Remuzzi G, Rapi S et al. Panethnic differences in blood pressure in Europe: A systematic review and meta-analysis. *PLOS ONE* 2016;11:e0147601.
  464. Whelton PK, Einhorn PT, Muntner P, Appel LJ, Cushman WC, Diez Roux AV et al. Research needs to improve hypertension treatment and control in African Americans. *Hypertension* 2016;68:1066–1072.
  465. Kaufman JS, Cooper RS, McGee DL. Socioeconomic status and health in blacks and whites: The problem of residual confounding and the resiliency of race. *Epidemiology* 1997;8:621–628.
  466. Agyemang C, van Oeffelen AA, Norredam M, Kappelle LJ, Klijn CJ, Bots ML et al. Socioeconomic inequalities in stroke incidence among migrant groups: Analysis of nationwide data. *Stroke* 2014;45:2397–2403.
  467. Mehanna M, Gong Y, McDonough CW, Beitelshes AL, Gums JG, Chapman AB et al. Blood pressure response to metoprolol and chlorthalidone in European and African Americans with hypertension. *J Clin Hypertens (Greenwich)* 2017;19:1301–1308.
  468. Erlinger TP, Vollmer WM, Svetkey LP, Appel LJ. The potential impact of nonpharmacologic population-wide blood pressure reduction on coronary heart disease events: Pronounced benefits in African-Americans and hypertensives. *Prev Med* 2003;37:327–333.
  469. Wright JT Jr, Dunn JK, Cutler JA, Davis BR, Cushman WC, Ford CE et al., ALLHAT Collaborative Research Group. Outcomes in hypertensive black and nonblack patients treated with chlorthalidone, amlodipine, and lisinopril. *JAMA* 2005;293:1595–1608.
  470. Wright JT Jr, Harris-Haywood S, Pressel S, Barzilay J, Baimbridge C, Bareis CJ et al. Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2008;168:207–217.
  471. Agyemang C, Nyaaba G, Beune E, Meeks K, Owusu-Dabo E, Addo J et al. Variations in hypertension awareness, treatment, and control among Ghanaian migrants living in Amsterdam, Berlin, London, and nonmigrant Ghanaians living in rural and urban Ghana – the RODAM study. *J Hypertens* 2018;36:169–177.
  472. Wijkman M, Lanne T, Engvall J, Lindstrom T, Ostgren CJ, Nyström FH. Masked nocturnal hypertension—a novel marker of risk in type 2 diabetes. *Diabetologia* 2009;52:1258–1264.
  473. Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): A multicentre, randomised, double-blind, controlled trial. *Lancet* 2008;372:547–553.
  474. Persson F, Lewis JB, Lewis EJ, Rossing P, Hollenberg NK, Parving HH. Aliskiren in combination with losartan reduces albuminuria independent of baseline blood pressure in patients with type 2 diabetes and nephropathy. *Clin J Am Soc Nephrol* 2011;6:1025–1031.
  475. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S et al., EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117–2128.
  476. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondur N et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644–657.
  477. Mancia G, Schumacher H, Redon J, Verdecchia P, Schmieder R, Jennings G et al. Blood pressure targets recommended by guidelines and incidence of cardiovascular and renal events in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET). *Circulation* 2011;124:1727–1736.
  478. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Matthews M et al., EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;375:323–334.
  479. Mancia G, Cannon CP, Tikkanen I, Zeller C, Ley L, Woerle HJ et al. Impact of empagliflozin on blood pressure in patients with type 2 diabetes mellitus and hypertension by background antihypertensive medication. *Hypertension* 2016;68:1355–1364.
  480. Buse JB. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:1798–1799.
  481. Bethel MA, Patel RA, Merrill P, Lokhnygina Y, Buse JB, Mentz RJ et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: A meta-analysis. *Lancet Diabetes Endocrinol* 2018;6:105–113.
  482. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels—overview and metaanalyses of randomized trials. *J Hypertens* 2014;32:2296–2304.
  483. Drawz PE, Alper AB, Anderson AH, Brecklin CS, Charleston J, Chen J et al., Chronic Renal Insufficiency Cohort Study Investigators. Masked hypertension and elevated nighttime blood pressure in CKD: Prevalence and association with target organ damage. *Clin J Am Soc Nephrol* 2016;11:642–652.
  484. Rossignol P, Massy ZA, Azizi M, Bakris G, Ritz E, Covic A et al., ERA-EDTA EURECA-m Working Group, Red de Investigación Renal (REDINREN) Network, Cardiovascular and Renal Clinical Trialists (F-CRIN INI-CRCT) Network. The double challenge of resistant hypertension and chronic kidney disease. *Lancet* 2015;386:1588–1598.
  485. Malhotra R, Nguyen HA, Benavente O, Mete M, Howard BV, Mant J et al. Association between more intensive vs less intensive blood pressure lowering and risk of mortality in chronic kidney disease stages 3 to 5: A systematic review and meta-analysis. *JAMA Intern Med* 2017;177:1498–1505.
  486. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S et al. Albuminuria, a therapeutic target for



- cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation* 2004;110:921–927.
487. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE et al., AIPRD Study Group. Progression of chronic kidney disease: The role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: A patient-level meta-analysis. *Ann Intern Med* 2003;139:244–252.
  488. Upadhyay A, Earley A, Haynes SM, Uhlig K. Systematic review: Blood pressure target in chronic kidney disease and proteinuria as an effect modifier. *Ann Intern Med* 2011;154:541–548.
  489. Sim JJ, Shi J, Kovesdy CP, Kalantar-Zadeh K, Jacobsen SJ. Impact of achieved blood pressures on mortality risk and end-stage renal disease among a large, diverse hypertension population. *J Am Coll Cardiol* 2014;64:588–597.
  490. Farsang CK, Kiss I, Tykarski A, Narkiewicz K. Treatment of hypertension in patients with chronic obstructive pulmonary disease (COPD). *European Society of Hypertension Scientific Newsletter* 2016;17:62.
  491. Baker JG, Wilcox RG. beta-Blockers, heart disease and COPD: Current controversies and uncertainties. *Thorax* 2017;72:271–276.
  492. Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-analysis: Effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths. *Ann Intern Med* 2006;144:904–912.
  493. Rutten FH, Zuithoff NP, Hak E, Grobbee DE, Hoes AW. Beta-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. *Arch Intern Med* 2010;170:880–887.
  494. Coiro S, Girerd N, Rossignol P, Ferreira JP, Maggioni A, Pitt B et al. Association of beta-blocker treatment with mortality following myocardial infarction in patients with chronic obstructive pulmonary disease and heart failure or left ventricular dysfunction: A propensity matched-cohort analysis from the High-Risk Myocardial Infarction Database Initiative. *Eur J Heart Fail* 2017;19:271–279.
  495. Cazzola M, Noschese P, D'Amato G, Matera MG. The pharmacologic treatment of uncomplicated arterial hypertension in patients with airway dysfunction. *Chest* 2002;121:230–241.
  496. Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: Updated systematic review and meta-analysis. *Lancet* 2016;387:435–443.
  497. Bangalore S, Messerli FH, Wun C, Zuckerman AL, DeMicco D, Kostis JB, LaRosa JC. Treating to New Targets Steering Committee and Investigators. J-Curve revisited: An analysis of the Treating to New Targets (TNT) Trial. *J Am Coll Cardiol* 2009;53:A217.
  498. Bangalore S, Qin J, Sloan S, Murphy SA, Cannon CP, PROVE IT-TIMI 22 Trial Investigators. What is the optimal blood pressure in patients after acute coronary syndromes?: Relationship of blood pressure and cardiovascular events in the PRavastatin OR atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT-TIMI) 22 trial. *Circulation* 2010;122:2142–2151.
  499. Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A et al. Dogma disputed: Can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006;144:884–893.
  500. Sleight P, Redon J, Verdecchia P, Mancia G, Gao P, Fagard R et al., ONTARGET Investigators. Prognostic value of blood pressure in patients with high vascular risk in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial study. *J Hypertens* 2009;27:1360–1369.
  501. Vidal-Petiot E, Ford I, Greenlaw N, Ferrari R, Fox KM, Tardif JC et al., CLARIFY Investigators. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: An international cohort study. *Lancet* 2016;388:2142–2152.
  502. Redon J, Mancia G, Sleight P, Schumacher H, Gao P, Pogue J et al., ONTARGET Investigators. Safety and efficacy of low blood pressures among patients with diabetes: Subgroup analyses from the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial). *J Am Coll Cardiol* 2012;59:74–83.
  503. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: Meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009;338:b1665.
  504. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure-lowering treatment. 6. Prevention of heart failure and new-onset heart failure-meta-analyses of randomized trials. *J Hypertens* 2016;34:373–384.
  505. Soliman EZ, Byington RP, Bigger JT, Evans G, Okin PM, Goff DC Jr, Chen H. Effect of intensive blood pressure lowering on left ventricular hypertrophy in patients with diabetes mellitus: Action to control cardiovascular risk in diabetes blood pressure trial. *Hypertension* 2015;66:1123–1129.
  506. Verdecchia P, Staessen JA, Angeli F, de Simone G, Achilli A, Ganau A et al., Cardio-Sis Investigators. Usual versus tight control of systolic blood pressure in nondiabetic patients with hypertension (CardioSis): An open-label randomised trial. *Lancet* 2009;374:525–533.
  507. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993–1004.
  508. Manning LS, Mistri AK, Potter J, Rothwell PM, Robinson TG. Short-term blood pressure variability in acute stroke: Post hoc analysis of the controlling hypertension and hypotension immediately post stroke and continue or stop poststroke antihypertensives collaborative study trials. *Stroke* 2015;46:1518–1524.
  509. Rodriguez-Luna D, Pineiro S, Rubiera M, Ribo M, Coscojuela P, Pagola J et al. Impact of blood pressure changes and course on hematoma growth in acute intracerebral hemorrhage. *Eur J Neurol* 2013;20:1277–1283.
  510. Sakamoto Y, Koga M, Yamagami H, Okuda S, Okada Y, Kimura K et al. Systolic blood pressure after intravenous antihypertensive treatment and clinical outcomes in hyperacute intracerebral hemorrhage: The stroke acute management with urgent risk-factor assessment and improvement-intracerebral hemorrhage study. *Stroke* 2013;44:1846–1851.
  511. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C et al., INTERACT2 Investigators. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med* 2013;368:2355–2365.
  512. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med* 2016;375:1033–1043.
  513. Tsvigoulis G, Katsanos AH, Butcher KS, Boviatsis E, Triantafyllou N, Rizos I, Alexandrov AV. Intensive blood pressure reduction in acute intracerebral hemorrhage: A meta-analysis. *Neurology* 2014;83:1523–1529.
  514. Ahmed N, Wahlgren N, Brainin M, Castillo J, Ford GA, Kaste M et al. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis: Retrospective analysis from Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). *Stroke* 2009;40:2442–2449.
  515. Wu W, Huo X, Zhao X, Liao X, Wang C, Pan Y et al. Relationship between blood pressure and outcomes in acute ischemic stroke patients administered lytic medication in the TIMS-China Study. *PLOS ONE* 2016;11:e0144260.
  516. Lee M, Ovbiagele B, Hong KS, Wu YL, Lee JE, Rao NM et al. Effect of blood pressure lowering in early ischemic stroke: Meta-analysis. *Stroke* 2015;46:1883–1889.
  517. Zhao R, Liu FD, Wang S, Peng JL, Tao XX, Zheng B et al. Blood pressure reduction in the acute phase of an ischemic stroke does not improve short- or long-term dependency or mortality: A meta-analysis of current literature. *Medicine (Baltimore)* 2015;94:e896.
  518. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM et al. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44:870–947.
  519. Sandset EC, Bath PM, Boysen G, Jatuzis D, Korv J, Luders S et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): A randomised, placebo-controlled, double-blind trial. *Lancet* 2011;377:741–750.
  520. Sandset EC, Murray GD, Bath PM, Kjeldsen SE, Berge E, Scandinavian Candesartan Acute Stroke Trial (SCAST) Study Group. Relation between change in blood pressure in acute stroke and risk of early adverse events and poor outcome. *Stroke* 2012;43:2108–2114.
  521. ENOS Trial Investigators. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): A partial-factorial randomised controlled trial. *Lancet* 2015;385:617–628.
  522. Robinson TG, Potter JF, Ford GA, Bulpitt CJ, Chernova J, Jagger C et al. Effects of antihypertensive treatment after acute stroke in the Continue or Stop Post-Stroke Antihypertensives Collaborative

- Study (COSSACS): A prospective, randomised, open, blinded-endpoint trial. *Lancet Neurol* 2010;9:767–775.
523. PATS Collaborating Group. Poststroke antihypertensive treatment study. A preliminary result. *Chin Med J (Engl)* 1995;108:710–717.
  524. White CL, Szychowski JM, Pergola PE, Field TS, Talbert R, Lau H et al., Secondary Prevention of Small Subcortical Strokes Study Investigators. Can blood pressure be lowered safely in older adults with lacunar stroke? The Secondary Prevention of Small Subcortical Strokes study experience. *J Am Geriatr Soc* 2015;63:722–729.
  525. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD et al., American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;45:2160–2236.
  526. Arima H, Chalmers J, Woodward M, Anderson C, Rodgers A, Davis S et al., PROGRESS Collaborative Group. Lower target blood pressures are safe and effective for the prevention of recurrent stroke: The PROGRESS trial. *J Hypertens* 2006;24:1201–1208.
  527. Collier DJ, Poulter NR, Dahlof B, Sever PS, Wedel H, Buch J, Caulfield MJ. Impact of amlodipine-based therapy among older and younger patients in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). *J Hypertens* 2011;29:583–591.
  528. National Institute for Health and Clinical Excellence. Hypertension (CG127): Clinical management of primary hypertension in adults. [www.nice.org.uk/guidance/CG127](http://www.nice.org.uk/guidance/CG127) (April 2018).
  529. Vickrey BG, Rector TS, Wickstrom SL, Guzy PM, Sloss EM, Gorelick PB et al. Occurrence of secondary ischemic events among persons with atherosclerotic vascular disease. *Stroke* 2002;33:901–906.
  530. Emdin CA, Rothwell PM, Salimi-Khorshidi G, Kiran A, Conrad N, Callender T et al. Blood pressure and risk of vascular dementia: Evidence from a primary care registry and a cohort study of transient ischemic attack and stroke. *Stroke* 2016;47:1429–1435.
  531. Ninomiya T, Ohara T, Hirakawa Y, Yoshida D, Doi Y, Hata J et al. Midlife and late-life blood pressure and dementia in Japanese elderly: The Hisayama study. *Hypertension* 2011;58:22–28.
  532. Sierra C, De La Sierra A, Salameo M, Sobrino J, Gomez-Angelats E, Coca A. Silent cerebral white matter lesions and cognitive function in middle-aged essential hypertensive patients. *Am J Hypertens* 2004;17:529–534.
  533. Snyder HM, Corriveau RA, Craft S, Faber JE, Greenberg SM, Knopman D et al. Vascular contributions to cognitive impairment and dementia including Alzheimer's disease. *Alzheimers Dement* 2015;11:710–717.
  534. Levi Marpillat N, Macquin-Mavier I, Tropeano AI, Bachoud-Levi AC, Maison P. Antihypertensive classes, cognitive decline and incidence of dementia: A network meta-analysis. *J Hypertens* 2013;31:1073–1082.
  535. Godin O, Tzourio C, Maillard P, Mazoyer B, Dufouil C. Antihypertensive treatment and change in blood pressure are associated with the progression of white matter lesion volumes: The Three-City (3C)-Dijon Magnetic Resonance Imaging Study. *Circulation* 2011;123:266–273.
  536. Lip GYH, Coca A, Kahan T, Boriani G, Manolis AS, Olsen MH et al. Hypertension and cardiac arrhythmias: A consensus document from the European Heart Rhythm Association (EHRA) and ESC Council on Hypertension, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). *Europace* 2017;19:891–911.
  537. Manolis A, Doumas M, Poulimenos L, Kallistratos M, Mancia G. The unappreciated importance of blood pressure in recent and older atrial fibrillation trials. *J Hypertens* 2013;31:2109–2117.
  538. Laukkanen JA, Khan H, Kurl S, Willeit P, Karppi J, Ronkainen K, Di Angelantonio E. Left ventricular mass and the risk of sudden cardiac death: A population-based study. *J Am Heart Assoc* 2014;3:e001285.
  539. Lip GY. Atrial fibrillation in patients with hypertension: Trajectories of risk factors in yet another manifestation of hypertensive target organ damage. *Hypertension* 2016;68:544–545.
  540. Conen D, Tedrow UB, Koplan BA, Glynn RJ, Buring JE, Albert CM. Influence of systolic and diastolic blood pressure on the risk of incident atrial fibrillation in women. *Circulation* 2009;119:2146–2152.
  541. Grundvold I, Skretteberg PT, Liestol K, Erikssen G, Kjeldsen SE, Arnesen H et al. Upper normal blood pressures predict incident atrial fibrillation in healthy middle-aged men: A 35-year follow-up study. *Hypertension* 2012;59:198–204.
  542. Freedman B, Potpara TS, Lip GY. Stroke prevention in atrial fibrillation. *Lancet* 2016;388:806–817.
  543. Schmieder RE, Kjeldsen SE, Julius S, McInnes GT, Zanchetti A, Hua TA, VALUE Trial Group. Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: The VALUE trial. *J Hypertens* 2008;26:403–411.
  544. Wachtell K, Lehto M, Gerds E, Olsen MH, Horneftam B, Dahlöf B et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: The Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. *J Am Coll Cardiol* 2005;45:712–719.
  545. Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667–1675.
  546. Ducharme A, Swedberg K, Pfeffer MA, Cohen-Solal A, Granger CB, Maggioni AP et al., CHARM Investigators. Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Am Heart J* 2006;152:86–92.
  547. Vermees E, Tardif JC, Bourassa MG, Racine N, Levesque S, White M et al. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: Insight from the Studies Of Left Ventricular Dysfunction (SOLVD) trials. *Circulation* 2003;107:2926–2931.
  548. GISSI-AF Investigators Disertori M, Latini R, Barlera S, Franzosi MG, Staszewsky L, Maggioni AP et al. Valsartan for prevention of recurrent atrial fibrillation. *N Engl J Med* 2009;360:1606–1617.
  549. Goette A, Schon N, Kirchhof P, Breithardt G, Fetsch T, Hausler KG et al. Angiotensin II-antagonist in paroxysmal atrial fibrillation (ANTIPAF) trial. *Circ Arrhythm Electrophysiol* 2012;5:43–51.
  550. Tveit A, Grundvold I, Olufsen M, Seljeflot I, Abdelnoor M, Arnesen H, Smith P. Candesartan in the prevention of relapsing atrial fibrillation. *Int J Cardiol* 2007;120:85–91.
  551. Nasr IA, Bouzamondo A, Hulot JS, Dubourg O, Le Heuzey JY, Lechat P. Prevention of atrial fibrillation onset by beta-blocker treatment in heart failure: A meta-analysis. *Eur Heart J* 2007;28:457–462.
  552. Swedberg K, Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Shi H et al., EMPHASIS-HF Study Investigators. Eplerenone and atrial fibrillation in mild systolic heart failure: Results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure) study. *J Am Coll Cardiol* 2012;59:1598–1603.
  553. Schaer BA, Schneider C, Jick SS, Conen D, Osswald S, Meier CR. Risk for incident atrial fibrillation in patients who receive antihypertensive drugs: A nested case-control study. *Ann Intern Med* 2010;152:78–84.
  554. Hung Y, Chao TF, Liu CJ, Tuan TC, Lin YJ, Chang SL et al. Is an oral anticoagulant necessary for young atrial fibrillation patients with a CHA2DS2-VASc score of 1 (men) or 2 (women)? *J Am Heart Assoc* 2016;5:e003839.
  555. Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW et al. Should atrial fibrillation patients with 1 additional risk factor of the CHA2DS2-VASc score (beyond sex) receive oral anticoagulation? *J Am Coll Cardiol* 2015;65:635–642.
  556. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893–2962.
  557. Zanchetti A, Crepaldi G, Bond MG, Gallus G, Veglia F, Mancia G et al., PHYLLIS Investigators. Different effects of antihypertensive regimens based on fosinopril or hydrochlorothiazide with or without lipid lowering by pravastatin on progression of asymptomatic carotid atherosclerosis: Principal results of PHYLLIS-a randomized double-blind trial. *Stroke* 2004;35:2807–2812.
  558. Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Volzke H, Tuomainen TP et al., PROG-IMT Study Group. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): A meta-analysis of individual participant data. *Lancet* 2012;379:2053–2062.
  559. Laurent S, Boutouyrie P, Vascular Mechanism Collaboration. Dose-dependent arterial destiffening and inward remodeling after olmesartan in hypertensives with metabolic syndrome. *Hypertension* 2014;64:709–716.



560. Ong KT, Delorme S, Pannier B, Safar ME, Benetos A, Laurent S, Boutouyrie P. Aortic stiffness is reduced beyond blood pressure lowering by short-term and long-term antihypertensive treatment: A meta-analysis of individual data in 294 patients. *J Hypertens* 2011;29:1034–1042.
561. Shahin Y, Khan JA, Chetter I. Angiotensin converting enzyme inhibitors effect on arterial stiffness and wave reflections: A meta-analysis and meta-regression of randomised controlled trials. *Atherosclerosis* 2012;221:18–33.
562. Ait-Oufella H, Collin C, Bozec E, Laloux B, Ong KT, Dufouil C et al. Long-term reduction in aortic stiffness: A 5.3-year follow-up in routine clinical practice. *J Hypertens* 2010;28:2336–2341.
563. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in endstage renal failure. *Circulation* 2001;103:987–992.
564. Singer DR, Kite A. Management of hypertension in peripheral arterial disease: Does the choice of drugs matter?. *Eur J Vasc Endovasc Surg* 2008;35:701–708.
565. Paravastu SC, Mendonca DA, da Silva A. Beta blockers for peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2009;38:66–70.
566. Radack K, Deck C. Beta-adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease. A meta-analysis of randomized controlled trials. *Arch Intern Med* 1991;151:1769–1776.
567. Nakamura K, Stefanescu Schmidt A. Treatment of hypertension in coarctation of the aorta. *Curr Treat Options Cardiovasc Med* 2016;18:40.
568. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H et al. ESC Committee for Practice Guidelines. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2014;35:2873–2926.
569. Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome. *N Engl J Med* 1994;330:1335–1341.
570. Groenink M, den Hartog AW, Franken R, Radonic T, de Waard V, Timmermans J et al. Losartan reduces aortic dilatation rate in adults with Marfan syndrome: A randomized controlled trial. *Eur Heart J* 2013;34:3491–3500.
571. Schaefer BM, Lewin MB, Stout KK, Gill E, Prueitt A, Byers PH, Otto CM. The bicuspid aortic valve: An integrated phenotypic classification of leaflet morphology and aortic root shape. *Heart* 2008;94:1634–1638.
572. Davies RR, Kaple RK, Mandapati D, Gallo A, Botta DM Jr, Elefteriades JA, Coady MA. Natural history of ascending aortic aneurysms in the setting of an unreplaced bicuspid aortic valve. *Ann Thorac Surg* 2007;83:1338–1344.
573. Lindman BR, Otto CM. Time to treat hypertension in patients with aortic stenosis. *Circulation* 2013;128:1281–1283.
574. Viigimaa M, Doumas M, Vlachopoulos C, Anyfanti P, Wolf J, Narkiewicz K, Mancia G. Hypertension and sexual dysfunction: Time to act. *J Hypertens* 2011;29:403–407.
575. Shamloul R, Ghanem H. Erectile dysfunction. *Lancet* 2013;381:153–165.
576. Dong JY, Zhang YH, Qin LQ. Erectile dysfunction and risk of cardiovascular disease: Meta-analysis of prospective cohort studies. *J Am Coll Cardiol* 2011;58:1378–1385.
577. La Torre A, Giupponi G, Duffy D, Conca A, Catanzariti D. Sexual dysfunction related to drugs: A critical review. Part IV: Cardiovascular drugs. *Pharmacopsychiatry* 2015;48:1–6.
578. Pickering TG, Shepherd AM, Puddey I, Glasser DB, Orazem J, Sherman N, Mancia G. Sildenafil citrate for erectile dysfunction in men receiving multiple antihypertensive agents: A randomized controlled trial. *Am J Hypertens* 2004;17:1135–1142.
579. Foy CG, Newman JC, Berlowitz DR, Russell LP, Kimmel PL, Wadley VG et al. Blood pressure, sexual activity, and dysfunction in women with hypertension: Baseline findings from the Systolic Blood Pressure Intervention Trial (SPRINT). *J Sex Med* 2016;13:1333–1346.
580. Jain M, Townsend RR. Chemotherapy agents and hypertension: A focus on angiogenesis blockade. *Curr Hypertens Rep* 2007;9:320–328.
581. Abi Aad S, Pierce M, Barmaimon G, Farhat FS, Benjo A, Mouhayar E. Hypertension induced by chemotherapeutic and immunosuppressive agents: A new challenge. *Crit Rev Oncol Hematol* 2015;93:28–35.
582. Maitland ML, Bakris GL, Black HR, Chen HX, Durand JB, Elliott WJ et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. *J Natl Cancer Inst* 2010;102:596–604.
583. Chang HM, Okwuosa TM, Scarabelli T, Moudgil R, Yeh ETH. Cardiovascular complications of cancer therapy: Best practices in diagnosis, prevention, and management: Part 2. *J Am Coll Cardiol* 2017;70:2552–2565.
584. Milan A, Puglisi E, Ferrari L, Bruno G, Losano I, Veglio F. Arterial hypertension and cancer. *Int J Cancer* 2014;134:2269–2277.
585. Aronson S, Mythen MG. Perioperative management of high-risk patients: Going beyond 'avoid hypoxia and hypotension'. *JAMA* 2017;318:1330–1332.
586. Kristensen SD, Knuuti J, Saraste A, Anker S, Botker HE, Hert SD et al. 2014 ESC/ESA Guidelines on noncardiac surgery: Cardiovascular assessment and management: The Joint Task Force on noncardiac surgery: Cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J* 2014;35:2383–2431.
587. Futier E, Lefrant JY, Guinot PG, Godet T, Lorne E, Cuvillon P et al. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: A randomized clinical trial. *JAMA* 2017;318:1346–1357.
588. Bouri S, Shun-Shin MJ, Cole GD, Mayet J, Francis DP. Meta-analysis of secure randomised controlled trials of beta-blockade to prevent perioperative death in noncardiac surgery. *Heart* 2014;100:456–464.
589. Blessberger H, Kammiller J, Domanovits H, Schlager O, Wildner B, Azar D et al. Perioperative beta-blockers for preventing surgery-related mortality and morbidity. *Cochrane Database Syst Rev* 2018;3:CD004476.
590. Zou Z, Yuan HB, Yang B, Xu F, Chen XY, Liu GJ, Shi XY. Perioperative angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers for preventing mortality and morbidity in adults. *Cochrane Database Syst Rev* 2016;1:CD009210.
591. Roshanov PS, Rochwerf B, Patel A, Salehian O, Duceppe E, BelleyCote EP et al. Withholding versus continuing angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers before noncardiac surgery: An analysis of the Vascular events In noncardiac Surgery patients cOhort evaluationN Prospective Cohort. *Anesthesiology* 2017;126:16–27.
592. London MJ, Hur K, Schwartz GG, Henderson WG. Association of perioperative beta-blockade with mortality and cardiovascular morbidity following major noncardiac surgery. *JAMA* 2013;309:1704–1713.
593. Andersson C, Merie C, Jorgensen M, Gislason GH, Torp-Pedersen C, Overgaard C et al. Association of beta-blocker therapy with risks of adverse cardiovascular events and deaths in patients with ischemic heart disease undergoing noncardiac surgery: A Danish nationwide cohort study. *JAMA Intern Med* 2014;174:336–344.
594. Kwon S, Thompson R, Florence M, Maier R, McIntyre L, Rogers T et al. Beta-blocker continuation after noncardiac surgery: A report from the surgical care and outcomes assessment program. *Arch Surg* 2012;147:467–473.
595. Chapman MJ, Ginsberg HN, Amarencu P, Andreotti F, Boren J, Catapano AL et al. European Atherosclerosis Society Consensus Panel. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: Evidence and guidance for management. *Eur Heart J* 2011;32:1345–1361.
596. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M et al. ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): A multicentre randomised controlled trial. *Lancet* 2003;361:1149–1158.
597. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ et al. JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195–2207.
598. Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L et al. HOPE-3 Investigators. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 2016;374:2021–2031.
599. . Authors/Task Force Members Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J* 2016;37:2999–3058.

600. Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, Amarenco P, Pedersen TR et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: A meta-analysis of statin trials. *J Am Coll Cardiol* 2014;64:485–494.
601. Brugs JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, Westendorp RG et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: Meta-analysis of randomised controlled trials. *BMJ* 2009;338:b2376.
602. Cholesterol Treatment Trialists' Collaboration Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B et al. Efficacy and safety of LDL-lowering therapy among men and women: Meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015;385:1397–1405.
603. Lip GY. Hypertension and the prothrombotic state. *J Hum Hypertens* 2000;14:687–690.
604. Lip GY, Felmeden DC, Dwivedi G. Antiplatelet agents and anticoagulants for hypertension. *Cochrane Database Syst Rev* 2011;12:CD003186.
605. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: The Swedish Atrial Fibrillation cohort study. *Eur Heart J* 2012;33:1500–1510.
606. Lip GY, Andreotti F, Fauchier L, Huber K, Hylek E, Knight E et al. Bleeding risk assessment and management in atrial fibrillation patients. Executive Summary of a Position Document from the European Heart Rhythm Association [EHRA, endorsed by the European Society of Cardiology [ESC] Working Group on. *Thrombosis Thromb Haemost* 2011;106:997–1011.
607. Lip GY, Lane DA. Bleeding risk assessment in atrial fibrillation: Observations on the use and misuse of bleeding risk scores. *J Thromb Haemost* 2016;14:1711–1714.
608. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA et al., LEADER Steering Committee, LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016;375:311–322.
609. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA et al., SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834–1844.
610. Birtwhistle RV, Godwin MS, Delva MD, Casson RI, Lam M, MacDonald SE et al. Randomised equivalence trial comparing three month and six month follow up of patients with hypertension by family practitioners. *BMJ* 2004;328:204.
611. Clark CE, Smith LF, Taylor RS, Campbell JL. Nurse led interventions to improve control of blood pressure in people with hypertension: Systematic review and meta-analysis. *BMJ* 2010;341:c3995.
612. Bray EP, Holder R, Mant J, McManus RJ. Does self-monitoring reduce blood pressure?. Meta-analysis with meta-regression of randomized controlled trials. *Ann Med* 2010;42:371–386.
613. Niiranen TJ, Hanninen MR, Johansson J, Reunanen A, Jula AM. Home-measured blood pressure is a stronger predictor of cardiovascular risk than office blood pressure: The Finn-Home study. *Hypertension* 2010;55:1346–1351.
614. Cook NR, Cutler JA, Obarzanek E, Buring JE, Rexrode KM, Kumanyika SK et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: Observational follow-up of the trials of hypertension prevention (TOHP). *BMJ* 2007;334:885–888.
615. Gupta AK, McGlone M, Greenway FL, Johnson WD. Prehypertension in disease-free adults: A marker for an adverse cardiometabolic risk profile. *Hypertens Res* 2010;33:905–910.
616. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D et al., DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *DASH-Sodium Collaborative Research Group. N Engl J Med* 2001;344:3–10.
617. Thompson AM, Hu T, Eshelbrenner CL, Reynolds K, He J, Bazzano LA. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: A metaanalysis. *JAMA* 2011;305:913–922.
618. Viera AJ, Bangura F, Mitchell CM, Cerna A, Sloane P. Do clinicians tell patients they have prehypertension? *J Am Board Fam Med* 2011;24:117–118.
619. Gale NK, Greenfield S, Gill P, Gutridge K, Marshall T. Patient and general practitioner attitudes to taking medication to prevent cardiovascular disease after receiving detailed information on risks and benefits of treatment: A qualitative study. *BMC Fam Pract* 2011;12:59.
620. Krousel-Wood M, Joyce C, Holt E, Muntner P, Webber LS, Morisky DE et al. Predictors of decline in medication adherence: Results from the cohort study of medication adherence among older adults. *Hypertension* 2011;58:804–810.
621. Mazzaglia G, Ambrosioni E, Alacqua M, Filippi A, Sessa E, Immordino V et al. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. *Circulation* 2009;120:1598–1605.
622. Burnier M, Wuerzner G, Struijker-Boudier H, Urquhart J. Measuring, analyzing, and managing drug adherence in resistant hypertension. *Hypertension* 2013;62:218–225.
623. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: Meta-analysis on 376,162 patients. *Am J Med* 2012;125:882–887;e1.
624. Tomaszewski M, White C, Patel P, Masca N, Damani R, Hepworth J et al. High rates of nonadherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. *Heart* 2014;100:855–861.
625. Berra E, Azizi M, Capron A, Hoieggan A, Rabbia F, Kjeldsen SE et al. Evaluation of adherence should become an integral part of assessment of patients with apparently treatment-resistant hypertension. *Hypertension* 2016;68:297–306.
626. Burnier M. Managing 'resistance': Is adherence a target for treatment? *Curr Opin Nephrol Hypertens* 2014;23:439–443.
627. Fletcher BR, Hartmann-Boyce J, Hinton L, McManus RJ. The effect of self-monitoring of blood pressure on medication adherence and lifestyle factors: A systematic review and meta-analysis. *Am J Hypertens* 2015;28:1209–1221.
628. Burnier M, Brede Y, Lowy A. Impact of prolonged antihypertensive duration of action on predicted clinical outcomes in imperfectly adherent patients: Comparison of aliskiren, irbesartan and ramipril. *Int J Clin Pract* 2011;65:127–133.
629. Lowy A, Munk VC, Ong SH, Burnier M, Vrijens B, Tousset EP, Urquhart J. Effects on blood pressure and cardiovascular risk of variations in patients' adherence to prescribed antihypertensive drugs: Role of duration of drug action. *Int J Clin Pract* 2011;65:41–53.



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