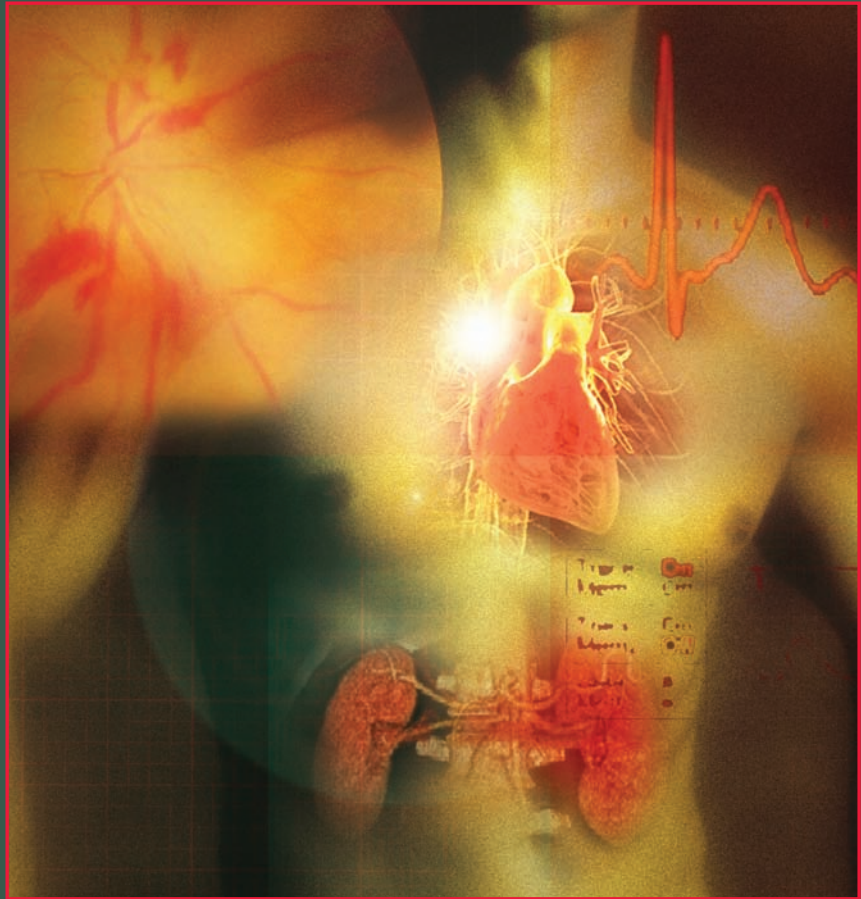


Hypertension

Domenic A. Sica • Peter P. Toth



FOREWORD BY SUZANNE OPARIL

CLINICAL PUBLISHING

CLINICAL CHALLENGES IN HYPERTENSION

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Contents

<i>Editors and Contributors</i>	vii
<i>Foreword</i>	ix
<i>Preface</i>	xi
1 What is endothelial cell dysfunction and does it impact capacity for vasodilatation? <i>P. P. Toth</i>	1
2 Sleep disorders and hypertension <i>C. C. Gonzaga, D. A. Calhoun</i>	17
3 Treatment of early morning surges in blood pressure <i>K. Kario</i>	27
4 Use of out-of-office blood pressure monitoring versus office-based measurements for managing patients with hypertension <i>N. Ghuman, W. B. White</i>	39
5 Is blood pressure control more important than decreasing activity in the renin-angiotensin axis? <i>W. J. Elliott</i>	51
6 Is there a class effect for all angiotensin-converting enzyme inhibitors when evaluating end-organ protection? <i>P. P. Toth, D. Sica</i>	63
7 Are angiotensin-receptor blockers equivalent or superior to ACE inhibitors relative to blood pressure control and/or end-organ protection? <i>R. R. Townsend</i>	79
8 Treatment of hypertension in the post-stroke patient in both the acute and chronic setting <i>W. J. Elliott</i>	89
9 Isolated systolic hypertension and management of hypertension in the very elderly <i>S. S. Franklin</i>	101

10	Management of hypertension in patients with coronary artery disease <i>C. Rosendorff</i>	115
	<i>List of abbreviations</i>	129
	<i>Index</i>	135

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Foreword

Hypertension is the most common form of cardiovascular disease in economically developed and developing countries, afflicting over 73 million persons in the US and over one billion worldwide. Left uncontrolled, it is a major contributor to death and disability due to stroke, coronary artery disease and chronic kidney disease. While blood pressure reduction has been shown in randomized controlled trials to be highly effective in preventing acute cardiovascular events and death, attainment of guideline specified blood pressure goals in the practice setting has proved difficult. Much of the difficulty experienced by primary care providers and hypertension specialists alike in managing blood pressure comes from conflicting information about the relative efficacy of various antihypertensive measures, both pharmacologic and nonpharmacologic (lifestyle modification). Further, there is a paucity of authoritative information about how to approach blood pressure management in patients with comorbidities that may be driving blood pressure elevation (anxiety and panic disorders, sleep disorders, athletic activities) or that may limit therapeutic choices (acute and chronic stroke, coronary artery disease) and in special patient populations (adolescents and young adults, the very elderly).

Edited by preventive cardiologist Peter Toth and clinical pharmacologist Domenic Sica, this new book fulfills an urgent need of those who care for hypertensive patients by providing answers or at least approaches to practical questions that are not addressed in current guidelines. The volume is organized around frequently asked questions about hypertension that surface time and time again at educational symposia. Issues discussed include both core clinical and scientific concepts and practical everyday patient related issues that are not well covered in most hypertension guidelines.

Chapters by world experts offer advice on such critical questions as: How should we use home (self) blood pressure measurement *vs* 24 hour ambulatory blood pressure monitoring *vs* office-based blood pressure readings for diagnosis and management of hypertension? What are appropriate treatment goals for systolic and diastolic blood pressure? In what patient groups? Does lifestyle modification play a major-and sustainable-role in hypertension management? If pharmacologic therapy is needed, does it matter what we use? Should we believe, as stated in JNC7, that diuretic therapy should be first step therapy in all (or nearly all) hypertensive patients? Or, should we adopt the recommendations of the more recent European guidelines that several classes of antihypertensive drugs are appropriate for first line treatment, at the discretion of the caregiver? What is more important, getting to goal blood pressure or blocking critical pathways, e.g., the renin-angiotensin-aldosterone system? In other words, when considering antihypertensive treatment, does mechanism matter? Are all angiotensin converting enzyme (ACE) inhibitors equally effective in lowering blood pressure? Protecting target organs? Are angiotensin receptor blockers (ARBs) equivalent or superior to ACE inhibitors in controlling blood pressure and protecting target organs? What is the best way to treat morning surges in blood pressure?

Importantly, there are many hypertensive patients for whom treatment recommendations based on the strongest form of evidence, the randomized controlled trial, are lacking.

Chapters in this book address many of these common and difficult to manage situations, e.g. the patient with anxiety/panic disorder and labile hypertension, the post-stroke (both acute and chronic) patient, the athlete who wishes to continue to compete despite his/her hypertension, the adolescent or young adult with hypertension in whom the short term risk of cardiovascular disease/events is low but the long term prognosis may not be benign, and the patient with a hypertensive emergency. For many of these conditions, there may never be randomized controlled trial data. In the meantime, the caregiver must rely on expert opinion and his/her own experience in caring for patients with these complex problems. *Clinical Challenges in Hypertension* is a treasure trove of valuable expert opinion on how to deal with many important problems in hypertension management. I recommend it highly.

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Preface

Hypertension (HTN) is a complex, multifactorial disease. In the last four decades an enormous amount of experimental, epidemiologic, and clinical investigation has demonstrated beyond all doubt that elevations in both systolic and diastolic blood pressure exert deleterious effects on the vasculature. Progressive injury stemming from chronically elevated blood pressure increases risk for developing endothelial dysfunction, loss of vascular elasticity and distensibility, atherosclerosis, left ventricular hypertrophy, heart failure, ischemic and hemorrhagic stroke, peripheral arterial disease, as well as proteinuria and nephropathy. Hypertension is widely prevalent throughout the world and constitutes a significant public health issue. The incidence of HTN is increasing in men and women and in people across all ethnic groups.

The treatment of hypertension is one of the true cornerstones in any approach to reducing risk for cardiovascular events in both the primary and secondary prevention settings. Evidence-based, population specific guidelines for the treatment of HTN have been developed by numerous expert bodies. These guidelines are rigorous and based on many well done prospective, randomized clinical trials. They emphasize the critical need to lower elevated blood pressure with lifestyle modification and pharmacologic intervention and to treat patients with end organ injury with specific classes of drugs. Despite the clarity and utility of many of these guidelines, there continues to be low rates of attaining target blood pressure in approximately two-thirds of the patients with HTN. Clearly, more focused efforts at improving the identification and management of HTN need to be implemented. Patient compliance and access to medication must also be improved.

The etiology of HTN depends on specific, highly complex genetic and metabolic backgrounds. Environmental influences (e.g. social/psychological stress, salt intake, diet) also play significant roles. The brain, kidney, and visceral adipose tissue regulate a wide range of biochemical and physiological responses which intimately influence the molecular and histologic dynamics of arterial walls, leading to increased vasomotor tone and HTN. Hypertension in any given individual is often multifactorial. During the last 60 years, many different drug classes have been developed to antagonize specific mechanisms by which blood pressure is raised (i.e. reducing intravascular volume, inhibiting renin and angiotensin converting enzyme, blocking intravascular catecholamine and angiotensin II receptors, and blocking calcium channels in smooth muscle cells). The majority of patients require combinations of drugs to control their blood pressure, especially in the presence of end organ damage. It requires clinical experience and insight into drug mechanisms to appropriately target specific mechanisms with specific drugs in order to optimally control blood pressure.

There are numerous fine textbooks in the field of hypertension and nephrology. This book is not intended to be encyclopedic. Rather, it is framed as a series of questions with detailed answers that are as evidence-based as possible. The authors are all experts in the field of HTN management. The questions posed are those that often arise at major conferences. These are the sorts of questions that often puzzle clinicians the most, or leave them

wondering what the evidence supporting certain approaches really consists of. Issues such as the need to treat early morning surges in blood pressure, the influence of sleep and anxiety disorders on blood pressure, determining the most efficacious first line agent for HTN, therapeutic equivalency of angiotensin converting enzymes and angiotensin receptor blockers, issues and complications in the management of isolated hypertension, and the nature of endothelial dysfunction, among others, receive detailed, focused, and practical treatment in a manner that emphasizes daily application in clinical and hospital settings. Therapeutic approaches emphasize established guidelines for HTN management. Important biochemical and physiologic pathways are illustrated. The emphasis of each chapter is on improving patient care and encouraging clinicians to expand their scope and efficacy of practice.

It is our sincerest wish that this book facilitates the mission each of us share in improving patient care. The targeted, appropriate management of HTN unequivocally reduces cardiovascular morbidity and mortality. The control of HTN also helps to forestall the development of endstage renal disease and need for dialysis and reduces the rate of progression of heart failure, atherosclerosis, and aortic aneurysms. Increasing the number of patients with well-controlled blood pressure is an important goal as it improves the quality and quantity of life. We hope that this book and its companion volume facilitate more aggressive and thoughtful approaches to blood pressure management.

Domenic Sica
Peter P. Toth

What is endothelial cell dysfunction and does it impact capacity for vasodilatation?

P. P. Toth

BACKGROUND

Atherosclerosis is a disease continuum that, without intervention, most often leads to coronary heart disease and cardiovascular events, including myocardial infarction, stroke, and sudden death. Dyslipidemia plays a major role in atherosclerosis, but so do other modifiable cardiovascular risk factors, including hypertension, insulin resistance and diabetes mellitus, and cigarette smoking. The vascular endothelium plays a pivotal role in the development of hypertension and atherogenesis. Endothelial cells represent a highly evolved cell type capable of an extraordinary range of both beneficial and, under certain conditions, injurious, biochemical functions. When impairment in local endothelial function increases the adhesiveness and permeability of the endothelium, monocytes and lipids infiltrate the underlying arterial intima, triggering pathogenic mechanisms that promote the formation of atherosclerotic plaques. An early and important part of this process is the reduced endothelial production of vasodilating substances and loss of normal vasomotor function. The endothelium is a critical modulator of blood pressure (BP) and vessel wall structure and function. Endothelial dysfunction is an area of intense clinical and scientific investigation. This chapter will examine the role of endothelial dysfunction in both hypertension and atherogenesis, two cardiovascular diseases that are tightly interwoven both clinically and mechanistically.

THE FUNCTIONAL ENDOTHELIUM

The vascular endothelium, a continuous monolayer of cells that lines the inner wall of blood vessels, including arterioles and capillaries, is one of the body's largest organ systems. It is estimated that if all of the endothelial cells in the human cardiovascular system were compiled into a single structure, they would form an organ about the size of a liver. By means of highly evolved, tightly sealed contacts between cells (i.e. 'gap junctions'), the endothe-

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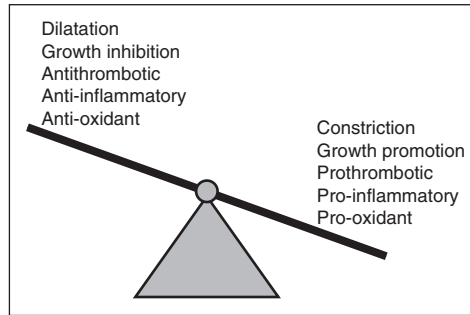


Figure 1.1 The endothelium maintains vascular health. In response to signals such as shear stress, endothelial cells produce and secrete vasoactive substances that can dilate or constrict blood vessels. Through these hemodynamic effects, the endothelium maintains blood pressure. Endothelial cells also produce and release substances that promote or inhibit growth and migration of vascular smooth muscle cells. Numerous substances released by the endothelium affect thrombosis, coagulation, and fibrinolysis. These include tissue plasminogen activator and plasminogen activator inhibitor-1. Endothelial cells also release substances that influence inflammation.

lium forms an impermeable barrier between circulating blood and body tissues. This barrier function helps to maintain the structural and functional integrity of arterial vessel walls.

The endothelium is far from inert: rather, it plays a key role in the events that determine the body's response to tissue injury. It is highly sensitive to biomechanical forces (e.g. shear stress) or biochemical stimuli (e.g. changes in bloodborne substances such as inflammatory mediators and trophic factors). In response to such signals, it synthesizes and releases messenger molecules such as nitric oxide (NO), endothelin, prostacyclin, and angiotensinogen, the precursor to angiotensin I and II (Ang I and II), which regulate vasoactivity and mitogenesis, thromboresistance, vascular permeability, platelet and inflammatory cell adhesion, and smooth muscle cell (SMC) proliferation and migration. In order to prevent thrombosis and luminal obstruction, the endothelium maintains a non-thrombogenic surface by producing tissue plasminogen activator (tPA) and other inhibitors of coagulation and thrombosis. Endothelial cells have sensors that regulate the cellular response to hypoxia; these include hypoxia-inducible factor (HIF)-1 alpha and mitochondria [1]. By maintaining a balance between opposing effects, the healthy endothelium preserves normal vascular physiology and homeostasis (Figure 1.1).

By synthesizing and releasing substances that relax or constrict the vessel, the endothelium regulates vascular tone and the vasomotion that maintains the active flow of oxygenated blood necessary for tissue perfusion throughout the body. Endothelial cells at various locations in the vascular tree may respond differently to bloodborne stimuli and express vasoactive substances to different degrees [2].

THE ROLE OF NITRIC OXIDE (NO)

In mediating vessel function, the most important substance expressed by the endothelium is NO. Nitric oxide may be considered an antiatherogenic, antiproliferative, and antithrombotic factor [3]. Originally described as endothelium-derived relaxing factor, NO is generated as a by-product of the conversion of the amino acid L-arginine to L-citrulline by the enzymatic action of the endothelial isoform of NO synthase (eNOS; Figure 1.2). Required cofactors include Ca^{2+} /calmodulin, flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN), and tetrahydrobiopterin (BH4) [4]. Blood flow across the endothelial cell surface (laminar shear stress) stimulates the expression of eNOS, so that organ perfusion is

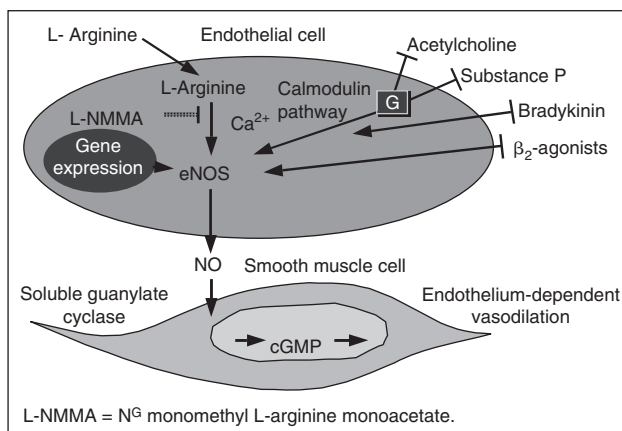


Figure 1.2 Endothelium-dependent vasodilation: L-arginine-nitric oxide pathway. Endothelial nitric oxide synthase (eNOS) is stimulated by blood flow across the endothelial cell surface (shear stress) or by chemical mediators that stimulate receptors on the endothelial cell surface. Nitric oxide (NO) diffuses to the underlying smooth muscle cells (SMC), where it stimulates guanylate cyclase to generate cyclic guanosine-5'-monophosphate (cGMP), which causes SMC relaxation and vasodilatation. Other regulators of NO production are substance P, bradykinin, and beta-agonists (with permission from [6]).

adapted to changes in cardiac output and local tissue oxygen demands [5]. Chemical mediators, including acetylcholine, bradykinin, adenosine, vascular endothelial growth factor (VEGF), substance P, and serotonin, also stimulate receptors on the endothelial cell surface [4, 6] (Figure 1.2). NO diffuses to vascular SMC in the tunica media, where it stimulates guanylate cyclase to generate cyclic guanosine-5'-monophosphate (cGMP), triggering SMC relaxation and vasodilatation [6].

EFFECTS OF NO

- Limits platelet aggregation and prevents platelet adhesion
- Inhibits leukocyte adhesion
- Prevents invasion of the vessel wall by monocytes and oxygen free radicals
- Inhibits proliferation and migration of vascular SMC into the intima, an early event in atherogenesis

Adequate supplies of NO help to ensure that balance between oxidative and anti-oxidative activity, cell quiescence and proliferation, and vasodilatation and vasoconstriction is maintained, and that normal vessel wall function is preserved.

Some endothelium-derived vasoactive factors, however, act independent of NO. These include the vasodilators prostacyclin [7] and endothelium-derived hyperpolarizing factor (EDHF) [8]. The contribution of EDHF, which appears to act predominantly in small arteries, is currently being actively investigated. In contrast, when endothelial cells become dysfunctional, they increase production of endothelin-1, a highly potent vasoconstrictor.

THE DYSFUNCTIONAL ENDOTHELIUM

A dysfunctional endothelium is one in which the activity and expression of NO are reduced, and endothelium-derived relaxation is impaired, creating an imbalance between relaxing and contracting factors. Under these conditions, the vessel wall is subject to constriction,

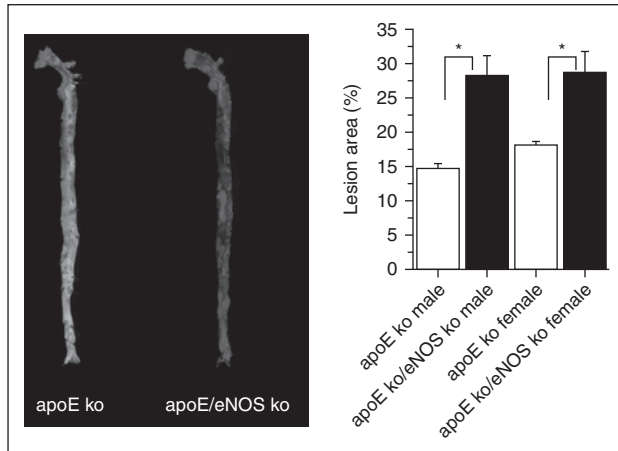


Figure 1.3 Deficiency of nitric oxide augments atherosclerosis in hypercholesterolemic mice. The left side of the figure shows longitudinally opened aortas from female apolipoprotein E (apoE)-knockout and apoE/eNOS-double knockout mice fed a Western-type diet for 16 weeks (luminal side, face up) displaying lipid-rich (darker) atherosclerotic lesions. The right side shows lesion areas at study end (lesion area/total area of the aorta) (with permission from [11]).

* = Significant difference ($P \leq 0.05$).

leukocyte adherence, platelet activation, mitogenesis in the media and adventitia, impaired capacity for anticoagulation and inhibition of platelet aggregation, and increased inflammation. If either of the key cofactors required for NO production, BH4 or calmodulin, is lacking, eNOS may ‘uncouple’, i.e. the superoxy ferrous-peroxy ferric complex may disassociate, yielding superoxide anion or hydrogen peroxide. These activated oxygen species can lead to increased lipid oxidation and peroxidation, which renders lipoproteins more atherogenic. In addition, superoxide anion and hydrogen peroxide can ‘quench’ NO, resulting in increased synthesis of peroxynitrite anions and reduced bioavailability of NO. All of these oxygen and nitrogen free radicals are also directly toxic to endothelial cells, potentially creating a vicious cycle whereby endothelial dysfunction becomes self-perpetuating and potentiates vessel wall injury, reduced vasodilatation (and hence hypertension), and atherogenesis [9].

ENOS DEFICIENCY AND ENDOTHELIAL DYSFUNCTION

Nitric oxide may be reduced either through decreased synthesis or through increased breakdown by oxidative mechanisms. Endogenous inhibitors of eNOS, including asymmetric dimethylarginine (ADMA), N-methylarginine (NMA), N(G)-monomethyl-L-arginine (L-NMMA), and N(G)-nitro-L-arginine methyl ester (L-NAME), accelerate atherosclerotic changes by shifting the balance between NO and oxygen-derived radicals in the direction of increased oxidative stress [10].

In a study conducted to test whether deficiency in eNOS affects the development of atherosclerosis, lesion formation was compared in apolipoprotein E (apoE)/eNOS double-knockout mice and apoE-knockout mice. After 16 weeks of a Western diet, the apoE/eNOS double-knockout mice showed coronary atherosclerosis associated with evidence of myocardial ischemia, myocardial infarction, and heart failure, but none of the apoE-knockout mice developed these complications. Male apoE/eNOS double-knockout mice also developed atherosclerotic abdominal aneurysms and aortic dissection. This study provides clear

evidence that in a murine model, eNOS deficiency initiates and accelerates the progression of atherosclerotic disease. The authors also point out that the BP effects of apoE deficiency and eNOS deficiency are not additive but reflect different degrees of endothelial dysfunction (Figure 1.3) [11].

REACTIVE OXYGEN SPECIES (ROS)

When eNOS is activated as a result of low shear stress, production of pro-oxidant enzymes is increased and the expression of anti-oxidant enzymes is decreased [12]. Signaling molecules, including bradykinin, adenosine, VEGF, and serotonin, may also play roles in this process [13, 14]. When NO expression is reduced, there is increased production of ROS secondary to increased expression of such pro-oxidative enzymes as xanthine oxidase (XO), cyclo-oxygenase, and nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase. Reactive oxygen species increase vascular permeability both by consuming NO and by inducing changes in the shape of endothelial cells [2]. Other damaging effects of ROS include a reduction in fibrinolytic capacity secondary to increased endothelial expression of plasminogen activator inhibitor-1 (PAI-1), increased platelet aggregation, the development of a procoagulant surface, proliferation of SMC, and accelerated atherogenesis. Inflammatory cytokines and interleukins, matrix metalloproteinases (which hydrolyze intercellular connective tissue proteins such as collagen and elastin), and lipid mediators may amplify the damaging effects of ROS [15].

Reactive oxygen species stimulate production of the potent vasoconstrictor endothelin-1 [16], further increasing BP and endothelial dysfunction. Xanthine oxidase is a major endothelial source of superoxide; endothelial XO levels are inversely related to endothelium-dependent vasodilatation and are increased in patients with coronary disease [17]. In patients with coronary artery disease, in whom endothelium-dependent vasodilatation was markedly reduced, intra-arterial infusion of oxypurinol (active metabolite of allopurinol), an inhibitor of XO, significantly improved flow-dependent endothelium-mediated vasodilatation before, but not after the angiotensin-receptor blocker (ARB) losartan or allopurinol [17].

In addition to increased production of ROS, endothelial dysfunction also results in decreased production of anti-oxidative enzymes. These include superoxide dismutase, which is involved in redox regulation of cellular function [15], glutathione reductase, which protects red blood cell enzymes and cell membranes against oxidative damage [18], and thioredoxin reductase, which maintains thiol-disulfide bond balance and helps protect various proteins from oxidative inactivation [19].

INFLAMMATION

In the setting of endothelial dysfunction, activation of the immune system induces the transcription of proinflammatory mediators in endothelial cells [9]. Chemokines and chemoattractants expressed by injured endothelial cells promote leukocyte (monocytes, T cells) recruitment and commit leukocytes to particular functional pathways [1, 20]. Generation of proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha, is augmented. TNF-alpha is expressed by macrophages and can stimulate the production of superoxide radicals [21, 22]. During the early stages of atherosclerosis, NADPH oxidase produces superoxide in the endothelium; in the more advanced stages of atherosclerosis, this process also occurs in vascular SMC [22]. Either TNF-alpha or IL-6 may induce secretion of IL-18 by macrophages, which has been shown to independently predict cardiovascular death in persons with coronary artery disease [1]. Under proinflammatory conditions, intra-vascular levels of lipoprotein-associated phospholipid (LP-PLA₂) may also increase. LP-PLA₂ is independently associated with coronary artery dysfunction and atherosclerosis, as this enzyme promotes the formation of toxic phospholipids and oxidized fatty acids [23].

ANGIOTENSIN II

Ang II is an active component of the renin-angiotensin system that is produced in the systemic circulation as well as in vascular and other tissues via the activity of angiotensin converting enzyme on Ang I. Ang II has the capacity to promote vasoconstriction, inflammation, thrombosis, and vascular remodeling [16].

EFFECTS OF ANG II INCLUDE

- Opposing NO-induced vasodilatation
- Activating ROS (eg, XO, NADPH oxidase) [17]
- Stimulating production of oxygen free radicals (eg, superoxide anion)
- Stimulating endothelial elaboration of endothelin-1
- Augmenting levels of IL-6 and monocyte chemotactic protein (MCP)-1, a cytokine that promotes the transmigration of inflammatory white cells from the endothelial surface into the subendothelial space
- Stimulating production of adhesion factors such as intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1
- Stimulating synthesis of PAI-1
- Inhibiting tPA secretion, and increasing coagulability and risk of thrombosis

Angiotensin II mediates most of its effects by activating the Ang II type-1 (AT₁) receptor, which, once turned on, elevates BP and initiates vascular dysfunction. The AT₁ receptor may also be upregulated by the acute-phase reactant C-reactive protein, which stimulates proliferation and migration of vascular SMC, neointimal formation, and production of ROS [1].

ADHESION MOLECULES AND PROTHROMBOTIC EFFECTS

Endothelial dysfunction decreases the expression of a blocker of two members of the TNF family, CD40 and its ligand, CD40L [1]. CD40L may be a molecular link between inflammation, thrombosis, and angiogenesis [24]. When CD 40 attaches to endothelial cells, adhesion molecules such as VCAM-1 and ICAM-1 are expressed, which promote the adherence of monocytes to the endothelial cell surface. ICAM-1, which is expressed on the surface endothelium, is constitutively expressed in the peripheral vasculature [20]. In experimental models of atherosclerosis, VCAM-1 mediates monocyte recruitment to early atherosclerotic lesions [20].

Platelets adhering to inflamed endothelium express the adhesion molecule P-selectin [25]. Leukocytes adhering to a lesion are then able to facilitate capture of other leukocytes from free flow plasma [20]. P-selectin may also induce the biosynthesis of tissue factor, an activator of platelet aggregation [12, 20, 25]. In addition to these well studied adhesion molecules, the roles of platelet endothelial cell adhesion molecule (PECAM)-1, CD99, junction adhesion molecules A, B, and C, and CD47 in atherosclerosis are being intensively investigated. An endothelium-derived glycoprotein, von Willebrand factor, can also be released into the circulation, where it promotes platelet activation as well as being a procoagulant [26].

CARDIOVASCULAR RISK FACTORS AND THE ENDOTHELIUM

Vascular homeostasis entails a delicate balance between cells that induce repair and those that produce damage, and conditions such as dyslipidemia, elevated BP, diabetes mellitus, cigarette smoking, and genetic factors, which may disrupt that equilibrium [12, 14]. All the major risk factors for cardiovascular disease are associated with reduced tissue BH4 levels, increased superoxide generation, and endothelial dysfunction, and all impair important cel-

lular functions [14]. Less severe injury may alter only one or two endothelial functions, whereas more extensive injury may alter several or all [27]. Multiple mechanisms may be responsible for reduced endothelium-dependent relaxation, but the principal cause is a lack or deficiency of NO, which also predisposes patients to atherosclerosis, coronary heart disease, hypertension, chronic heart failure, and vasculopathies associated with diabetes mellitus. [28]

DYSLIPIDEMIA

In the presence of hypercholesterolemia the endothelium promotes vasoconstriction, monocyte and platelet adhesion, thrombogenesis, and growth factor release (e.g., platelet-derived growth factor, fibroblast growth factor) [29]. Hypercholesterolemia is an important initiator of atherogenesis, which begins at sites of endothelial dysfunction and is exacerbated by increased levels of low-density lipoprotein cholesterol (LDL-C). As the dysfunctional endothelium becomes permeable, monocytes accumulate in the intima. In response to monocyte colony stimulating factor, monocytes differentiate into macrophages resident in the subendothelial space. As macrophages are exposed to oxidized lipids and phospholipids, they express families of scavenging receptors (scavenger receptor A and CD36, among others) on their surface and progressively take up more and more lipid, eventually becoming foam cells. Foam cells produce cytokines, matrix metalloproteinases, ROS, and procoagulant tissue factor. The foam cells can coalesce and turn into fatty streaks, which progressively increase in volume, forming the lipid core of an atheromatous lesion. SMCs proliferate, stimulated by inflammatory cytokines and growth factors produced within atheromatous plaques, and secrete extracellular matrix material that forms a fibrous cap over the core [30]. The dysfunctional endothelium further increases cardiovascular risk by promoting local shear stress, which increases the risk of plaque rupture [31]. When an atherosclerotic plaque ruptures, circulating platelets are exposed to tissue factor, adenosine 5'-diphosphate, and collagen, which promote activation, aggregation, and the formation of an obstructive thrombus within the lumen of the involved artery.

As the endothelium becomes dysfunctional and expression of eNOS at the vessel wall is reduced, superoxide is generated, and oxidative stress is increased, further impairing endothelium-dependent relaxation [32]. Whereas in hypercholesterolemia loss of endothelial-dependent vasodilatation is selective, in advanced atherosclerosis, it is complete [33].

Elevated lipid levels are associated with a significant overexpression of AT₁ receptors along the endothelial surface, leading to a substantial increase in Ang-II-induced BP elevations. Nickenig *et al.* conducted a study to examine AT₁ receptor overexpression in hypercholesterolemic men and the effect on BP of lipid-lowering therapy. Effects of hypercholesterolemia on AT₁ receptor activation were determined by measuring changes in BP after the infusion of Ang II in men with normal cholesterol ($n = 19$) and hypercholesterolemia (294 ± 10 mg/dL; $n = 20$). The data suggested that high levels of LDL-C exaggerate BP responses to Ang II related to increased endothelial expression of AT₁ receptors (Figure 1.4) [34].

HYPERTENSION

Normal coronary vasodilatation is impaired in hypertensive persons as a result of not only BP elevation but also as a function of inflammation and oxidative stress induced by degradation of NO, activation of endothelin-1, and other vasoactive substances, including bradykinin and prostacyclin. Reduced production of NO and/or EDHF may diminish endothelium-dependent relaxation, promoting net vasoconstriction [35].

The renin-angiotensin system is central to many pathologic processes leading to cardiovascular events, and constriction of the systemic vasculature by Ang II leads to hyperten-

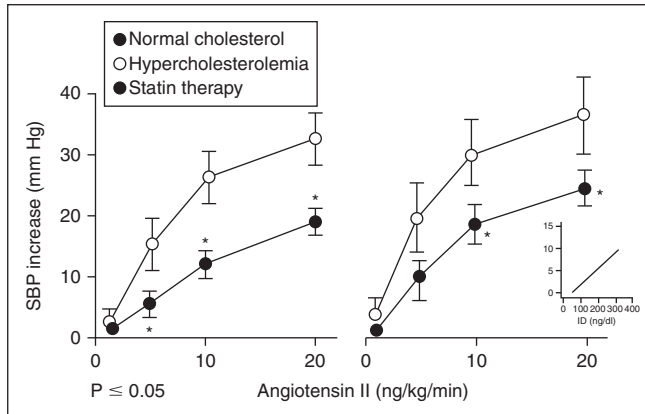


Figure 1.4 Hypercholesterolemia induces AT_1 receptor expression. Left side: The effect of an infusion of angiotensin II (Ang II) in normal and hypercholesterolemic individuals ($n = 8$). Right side: Measurements in hypercholesterolemic individuals before and after treatment with 20–40 mg atorvastatin or simvastatin for 6 weeks. The inset figure shows the significant correlation between the Ang II type-1 (AT_1) receptor density on isolated platelets and low-density lipoprotein cholesterol (LDL-C) plasma concentrations. The data indicate that hypercholesterolemia stimulates AT_1 receptor overexpression and causes a more profound increase in Ang II-induced blood pressure elevation, and that treatment with statins can reduce Ang-II-induced elevations in blood pressure (with permission from [34]).

sion. In the kidney, Ang II causes sodium and water retention and efferent arteriolar vasoconstriction. Hypertension is associated as well with activation of rho kinase. In *in vitro* studies, rho kinase has been shown to play a role in SMC contraction, and activation of rho kinase in vascular SMCs may be involved in the development of atherosclerosis [36].

Because eNOS plays an important role in the recruitment of inflammatory cells, oxidative stress, and vascular response to injury, it has been postulated that eNOS deficiency could be one of the mechanisms linking hypertension to atherosclerosis [11]. Other mechanisms include deposition of abnormal forms of collagen and elastin, calcification, scarring, increased thickness in the smooth muscle cell layer comprising the media, and thickening of the adventitia, all of which can potentiate a loss of vessel wall distensibility and compliance.

DIABETES MELLITUS

In insulin-sensitive individuals, as much as two-thirds of insulin-mediated vasodilatation derives from signaling mechanisms in the endothelium [37].

BENEFICIAL EFFECTS OF INSULIN

- Augments NO bioavailability
- Suppresses generation of ROS
- Reduces plasma concentrations of adhesion molecules
- Reduces proinflammatory factors in plasma (eg, VEGF, matrix metalloproteinase-9) [38]
- Reduces PAI-1

As a result of increased production of ROS, insulin-induced NO production is reduced or lacking in insulin-resistant or diabetic individuals. In insulin-resistant conditions, vasodila-

tation is impaired and arterial pressure is elevated, resulting in endothelial dysfunction, worsening insulin resistance, and macrovascular disease. In early diabetic vasculopathy, oxidative stress increases vascular permeability, allowing monocytes to move between endothelial cells and migrate into the wall of the artery [39].

Nonenzymatic protein glycation is a process that yields toxic compounds known as advanced glycation end-products (AGEs), which have been implicated in the pathogenesis of diabetic vascular complications [40]. In insulin resistance and diabetes mellitus, AGEs bind to endothelial cell surface receptors for AGE (RAGE), generating ROS and inducing the expression of adhesion molecules, tissue factor, and foam cells independent of diabetic hyperglycemia [41].

CIGARETTE SMOKING

Cigarette smoke induces vascular dysfunction by increasing vascular production of superoxide anion, which inactivates NO. It contains high concentrations of peroxynitrite, peroxynitrate, and thiol-reactive substances, all of which may adversely effect the vasculature [42]. Cigarette smoke may also contribute to endothelial dysfunction by activating rho kinase in vascular SMC [36]. This dysfunction is not limited to the pulmonary circulation, but also occurs in the systemic circulation [42]. In a study in healthy young men, intra-arterial infusion of sodium nitroprusside, a direct vasodilator of vascular smooth muscle, increased plethysmographically measured forearm blood flow equivalently in smokers and in non-smokers; alternatively, forearm blood flow response to acetylcholine, which dilates healthy arteries, was significantly reduced in smokers compared to nonsmokers ($P < 0.01$) [36].

REPAIRING THE DAMAGED ENDOTHELIUM

LOCAL MITOGENESIS

Mature endothelial cells have the capacity to replicate locally, replacing cells that have been damaged or destroyed. Under normal conditions the integrity and continuity of the endothelium can be maintained in this manner. However, in the presence of cardiovascular risk factors, these cells cannot replicate quickly enough and additional means are required to repair the damaged endothelium [43].

ENDOTHELIAL PROGENITOR CELLS

The differentiation of endothelial precursor cells, or angioblasts, into endothelial cells, is a key mechanism in normal vascular development [44]. In adults, endothelial progenitor cells are thought to be derived from CD34 hematopoietic stem cells that originate in bone marrow. They migrate through the endothelial barrier and thereafter are blood borne. When they reach an anatomical defect along an endothelial surface, they invade target tissue. There they differentiate into mature endothelial cells, a process known as vasculogenesis that can occur both in embryos and in adults [12, 44]. The same factors that improve the bioavailability of NO also improve the mobilization and homing of endothelial progenitor cells [44]. Growth factors such as VEGF, cytokines, and chemoattractants all play important roles in this process. Because the expression of anti-oxidant enzymes is higher in endothelial progenitor cells than in mature endothelial cells, artificially increasing numbers of endothelial progenitor cells could potentially be therapeutic, particularly in the instance of myocardial ischemia [12, 45].

STATINS

In recent years, HMG-CoA reductase inhibitors (statins) have been shown to have numerous 'pleiotropic' effects unrelated to their lipid-lowering properties.

Effects of statins

- Inhibit oxidation of low-density lipoprotein, a key step in atherogenesis
- Stabilize mRNA transcripts for eNOS activity, increasing endothelial NO activity
- Stimulate production of tPA
- Inhibit cytokine production
- Inhibit the activity of NADH oxidase
- Downregulate expression of the AT₁ receptor, attenuating Ang II-induced free radical production in vascular SMC and induction of vasoconstriction [46]
- Inhibit the expression of endothelin-1
- Improve endothelium-dependent vasomotion in large arteries and resistance vessels [33]

Improved endothelial function has been shown after only 2 weeks of statin use [46]. In two small studies, statin therapy improved endothelium-dependent dilatation in the forearm circulation [47, 48]. In the study by Nickenig *et al.* discussed above, lipid-lowering therapy with statins (20 to 40 mg of atorvastatin or simvastatin), caused a significant decrease in the Ang II induced BP increase ($P < 0.05$) and downregulated AT₁ receptor density in isolated platelets ($P < 0.05$) (Figure 1.4) [34]. In the randomized, double-blind Coronary Artery Reactivity After Treatment with Simvastatin (CARATS) study, however, 6 months of treatment with simvastatin improved the lipid profile but failed to show a significant improvement in coronary endothelial vasomotor function compared with placebo in 60 patients with coronary artery disease and mildly elevated cholesterol levels [49]. The investigators proposed that the relatively mild degree of endothelial function at baseline in this patient population might explain these results.

ANTIHYPERTENSIVE MEDICATIONS

Various antihypertensive drugs have shown favorable effects on the endothelium.

Alpha, beta blockers

Combination alpha, beta-blockers such as carvedilol have anti-oxidant activity that may improve endothelial function. In one study, 28 patients with coronary artery disease were randomized to carvedilol or placebo. Using high-resolution ultrasound, brachial flow-mediated dilatation was assessed during reactive hyperemia and after nitroglycerin-induced endothelium-independent dilatation. Although there were no significant changes in endothelium-independent dilatation with either placebo or carvedilol in response to reactive hyperemia after 2 h, after 4 months, treatment with carvedilol significantly increased flow-mediated dilatation compared with both baseline ($P < 0.01$) and placebo values ($P < 0.01$). The improvement in endothelial function was not likely due to the BP-lowering effect of carvedilol, since BP reduction of a similar magnitude (to what was observed in these studies) with different antihypertensive agents has had a limited effect on endothelial dysfunction [32].

Calcium-channel blockers

Calcium-channel blockers induce vasorelaxation by blocking calcium ion influx into vascular smooth muscle. They also stimulate the release of VEGF from vascular smooth muscle and induce angiogenesis. In addition to beneficial effects on the endothelium, calcium-channel blockers exert anti-oxidant effects on endothelial precursor cells. When precursor cells were exposed to nifedipine, they were more resistant to cellular oxidant stress, dysfunction, and apoptosis mediated by hydrogen peroxide [45]. In patients with Stage 1 hypertension,

nifedipine (4 weeks of treatment with 20-mg sustained-release) stimulates NO production and preserves endothelial function [45].

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors block the formation of Ang II. They also reduce the degradation of bradykinin and improve the biosynthesis of NO and prostacyclin, all vasodilators. These effects collectively result in improved vasodilatation and BP reduction [33].

A randomized, double-blind, crossover study was conducted to determine whether and by how much simvastatin or enalapril, separately or combined, could modify endothelial function [33]. In this study, 38 hypercholesterolemic patients were treated with either simvastatin or enalapril, for 8 weeks and with both drugs for another 8 weeks. Brachial artery diameter was measured before and after postischemic hyperemia using high-resolution ultrasound at baseline and at 8 and 16 weeks. In the group receiving simvastatin first, after the first 8 weeks, endothelium-dependent vasodilatation significantly increased ($P < 0.001$), and the addition of enalapril further improved vasodilatation at 16 weeks. In the group receiving enalapril first, at 8 weeks vasodilatation improved compared with control ($P < 0.01$), and further improvement was seen at 16 weeks with the addition of simvastatin ($P < 0.001$ vs 8 weeks). Thus, both agents improved the postischemic vasodilator response and additive effects were seen with the combination of both [33].

In the Trial on Reversing Endothelial Dysfunction (TREND), the angiotensin-converting enzyme inhibitor quinapril in normotensive individuals with coronary artery disease improved endothelium-mediated vasodilatation as assessed by intracoronary administration of acetylcholine, independent of antihypertensive effects [50].

Angiotensin-receptor blockers (ARBs)

Some, although possibly not all, ARBs have anti-oxidant properties. The ability to inhibit superoxide production mediated by Ang II has been seen with olmesartan but not with losartan [51]. However, losartan and other ARBs may prevent NADPH oxidase-dependent superoxide production and activation of XO [17]. In addition, ARBs may increase scavenging of superoxide by extracellular superoxide dismutase [17]. Olmesartan may help prevent myocardial infarction by maintaining low coronary vascular resistance during high flow demand situations.

Cold pressor testing measures changes in BP or heart rate in response to immersion of the hand in ice water for 60 to 120 seconds: sympathetic activation leads to vasoconstriction and elevated pulse pressure. In one study, 26 hypertensive patients were randomized to olmesartan or the calcium-channel blocker amlodipine for 12 weeks. Myocardial blood flow at rest and during cold pressor testing were determined using positron emission tomography. Before treatment, myocardial blood flow significantly decreased from rest to the cold pressor test. After treatment, olmesartan but not amlodipine improved endothelium-dependent coronary dilatation, despite the fact that BP reduction was comparable in the two groups [51]. Activity of the anti-oxidative enzyme superoxide dismutase also increased in the olmesartan group.

Other

Several additional strategies have been proposed, with greater or less success, in an effort to restore damaged endothelium to a functional state.

Anti-oxidant vitamins

In principle, since ROS trigger endothelial dysfunction, anti-oxidants should inhibit their activity and even repair endothelial injury. However, anti-oxidants have shown little or no

benefit in reducing clinical outcomes. In the Medical Research Council (MRC)/British Heart Foundation (BHF) Heart Protection Study, more than 20 000 patients were randomized to placebo or to a daily regimen of 20-mg of beta-carotene, 250-mg of vitamin C, and 600-mg of vitamin E. The anti-oxidant regimen produced no significant reduction in cardiovascular events despite this regimen substantially increasing blood vitamin levels [52].

Reducing XO activation

Selective modulation of XO signaling has been proposed as a therapeutic target: allopurinol has been shown to prevent the production of superoxides as well as to attenuate ischemia/reperfusion injury induced by XO activation [21]. However, although allopurinol reduced the activity of XO and improved endothelium-dependent vasodilatation, the ARB losartan had a more pronounced effect [17].

High-density lipoprotein (HDL)

High-density lipoprotein is known to attenuate the formation of oxidized LDL and to stabilize prostacyclin, but it may also augment the ability of the endothelium to increase eNOS expression, thereby enhancing vasorelaxation. Flow-mediated dilatation was improved in eleven patients with coronary artery disease and well controlled LDL-C after HDL cholesterol levels were raised (30.1 ± 1.2 to 40.5 ± 1.2 mg/dL) by oral administration of niacin for 3 months [53].

BH4

Supplementation with exogenous BH4 could potentially restore NO activity in patients with coronary artery disease, hypercholesterolemia, or diabetes [9]. In mice, incubation of vessels with sepiapterin, a precursor to BH4, improved endothelial-dependent relaxation and decreased superoxide production. [22].

Glitazones

Thiazolidinediones activate eNOS. In an animal model, pioglitazone inhibited Ang II-induced peroxynitrite formation and senescence of endothelial progenitor cells. [54] Treatment with rosiglitazone significantly improved flow-mediated dilatation of the brachial artery in young women with polycystic ovary syndrome after 6 months, comparable with what was seen with metformin [55].

MEASURING ENDOTHELIAL DYSFUNCTION AND REPAIR

Coronary endothelial dysfunction is an independent long-term predictor of atherosclerotic disease progression and coronary heart disease event rates [56]. A correlation between vascular function in the coronary and peripheral vasculature suggests that the endothelium functions through common pathways in both vascular beds [57]. Because blood flow shear stress stimulates the release of NO, measurement of forearm blood flow responses to vasoactive agents indicates endothelial function in conduit arteries [36]. Acetylcholine can dilate healthy arteries by stimulating the release of NO. In patients with coronary artery disease or risk factors, however, acetylcholine administration may cause paradoxical vasoconstriction and impaired flow-mediated vasodilatation, reflecting endothelial dysfunction [58].

Several tests have been developed to evaluate endothelial-dependent vasomotion and/or physiologic stimulation of endothelial NO release. These tests may also reveal early atherosclerosis that may not yet be detectable angiographically [58]. Veno-occlusion plethysmography tests acetylcholine response in the forearm using mercury strain gauges during hyperemia. This test is currently the gold standard for clinical research on endothelial function [14]. Brachial artery imaging with high resolution ultrasound during reactive hypere-

mia has been used, but its lack of standardized methodology has made it less useful clinically [57]. Another type of testing involving infusion of eNOS inhibitors requires brachial artery cannulation and so is less useful clinically [57].

Circulating biomarkers have also been used to assess endothelial function: these include ADMA, a competitive antagonist of eNOS, which is linked to preclinical atherosclerotic disease, an imbalance in levels of tPA and PAI-1, and von Willebrand factor. In a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), elevated levels of P-selectin were predictive of myocardial infarction in high-risk hypertensive patients, but levels of von Willebrand factor were not associated with coronary events, and neither marker predicted cerebrovascular or composite cardiovascular endpoints [59].

Since nearly all risk factors for atherosclerosis decrease the number of circulating endothelial cells, the number of these cells could reflect endothelial injury and predict cardiovascular events [45]. This may be measured using flow cytometry or fluorescent microscopy. In addition, circulating cellular proteins, inflammatory markers, or adhesion molecules that were shed from the surface of damaged endothelial cells may be markers of cardiovascular risk. These may include metabolites of NO excreted in urine, C-reactive protein, or reduced levels of extracellular superoxide dismutase. However, to date there is no evidence that alterations in any biomarker correlate specifically with endothelial dysfunction [27].

Although endothelial function testing can provide prognostic value independently of that provided by assessment of traditional risk factors, to date all tests of endothelial function remain too expensive and too variable for routine clinical use. A simple, inexpensive, and standardized test that would detect early and progressive endothelial dysfunction is urgently needed [27].

SUMMARY

The vascular endothelium is a dynamic, versatile, and complex organ that is highly responsive to its environment. It plays a pivotal role in maintaining normal BP, vascular homeostasis, and protecting the vasculature from inflammatory and prothrombotic changes that could lead to cardiovascular morbidity and mortality. The healthy endothelium produces factors that regulate numerous beneficial effects including vasodilatation and protecting the vessel wall from inflammatory and oxidative injury. Injuries to the endothelium caused by atherosclerosis, hypertension, diabetes mellitus, cigarette smoking, and other cardiovascular risk factors adversely affect cellular function, create an imbalance between relaxing and contracting factors in the endothelium, and further exacerbate endothelial dysfunction, hypertension, and vascular disease. Meticulous control of cardiovascular risk factors helps to prevent endothelial dysfunction and the development and progression of cardiovascular disease.

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Sleep disorders and hypertension

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BACKGROUND

A large body of evidence links sleep-disordered breathing to the development and severity of hypertension. Obstructive sleep apnea (OSA) is now recognized as a common potentially reversible cause of hypertension, particularly in patients with resistant hypertension. As older age and obesity are common risk factors for development of OSA, the prevalence of OSA is anticipated to increase as populations worldwide undergo increases in age and weight.

Signs and symptoms of OSA include disruptive snoring, frequent nocturnal arousals, witnessed apnea, excessive daytime sleepiness, obesity, and an enlarged neck size. Accordingly, the medical interview of hypertensive patients should include questions related to sleep and the possible presence of OSA.

Obstructive sleep apnea can, in most cases, be effectively treated with continuous positive airway pressure (CPAP). Adjunctive therapies include postural adjustments, weight loss, and alcohol avoidance. Adherence with CPAP is often poor and so its use should be monitored and if deficient addressed by the treating sleep specialist.

DEFINITION

OSA is characterized by repetitive interruption of breathing during sleep secondary to collapse of the pharyngeal airway [1]. An obstructive apnea is a ≥ 10 -second pause in respiration during ongoing ventilatory effort. Obstructive hypopneas are decreases in, but not complete cessation, of respiration with an associated fall in oxygen saturation or an arousal. A diagnosis of OSA syndrome is made when a patient has an apnea-hypopnea index (AHI; number of apneas and hypopneas per hour of sleep) > 5 and symptoms of excessive daytime sleepiness and/or associated comorbidities including hypertension, coronary heart disease, mood disorders, or cognitive decline.

Pharyngeal collapse in patients with OSA generally occurs posterior to the tongue, uvula, and soft palate. This portion of the pharyngeal airway has relatively little bony or rigid support and is therefore largely dependent on muscle activity to maintain patency. The primary

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Table 2.1 Obstructive sleep apnea signs, symptoms, and risk factors

Disruptive snoring
Witnessed apnea or gasping
Obesity and/or enlarged neck circumference (>17 inches in men and >15 inches in women)
Excessive daytime sleepiness
Other signs and symptoms include male gender, crowded pharyngeal airway, hypertension, morning headache, sexual dysfunction, behavioral changes (especially in children)

abnormality in patients with OSA is an anatomically small pharyngeal airway resulting from obesity, bone and soft tissue structures, or, in children, tonsils and adenoids [2]. During wakefulness, this leads to increased airflow resistance and greater intrapharyngeal negative pressure during inspiration. Mechanoreceptors located primarily in the larynx respond reflexively to this negative pressure and increase the activity of a number of pharyngeal dilator muscles, thereby maintaining airway patency while awake [2, 3]. However, during sleep, the reflex pharyngeal muscle activity that drives this neuromuscular compensation is reduced or lost, leading to reduced dilator muscle activity and ultimately to pharyngeal narrowing and intermittent complete collapse. [4] During the subsequent apnea or hypopnea, hypoxia and hypercapnia stimulate ventilatory effort and ultimately arousal from sleep to terminate the apneic event. Thus, an upper airway that requires reflex-driven muscle activation to maintain patency during wakefulness may be vulnerable to collapse during sleep [1].

PREVALENCE

The high prevalence and wide spectrum of severity of OSA in adults has been well documented by multiple population-based cohort studies conducted in the United States, Europe, Australia, and Asia [1]. Most of these studies have shown that approximately 20% of adults have at least mild OSA (e.g. AHI ≥ 5 events/hr) and 7% have moderate or severe OSA (e.g. AHI ≥ 15 events/hr) [5]. However, most OSA remains undetected with an estimated 85% of patients with clinically significant and treatable OSA having never been diagnosed [6].

CLINICAL PRESENTATION

The prevalence of OSA is twice as high in men than in women [5]. Patients may present with a number of signs and symptoms suggestive of the disorder (Table 2.1) or with no symptoms whatsoever [1]. However, clinical judgment ultimately must be used in deciding which patients deserve further evaluation. For example, virtually all patients with OSA snore, but not all snorers have sleep apnea.

The prevalence of OSA is increased in patients with cardiovascular (CV) disease including hypertension, coronary heart disease, atrial fibrillation, and heart failure (HF) and may contribute to progression of these diseases. Accordingly, evaluation for and treating OSA if present may be particularly relevant in these patients. However, at the present time, this does not mean that all patients with cardiovascular disease should undergo formal testing for OSA. If other indicators also are present (witnessed apneas, disruptive snoring, obesity, hypersomnolence) or if the CV condition is refractory to standard therapy, there should be a low threshold for pursuing the diagnosis [1].

Screening of patients for OSA can be accomplished by several different methods, although the sensitivity and specificity of these have not been well documented, particularly in CV patients, and will be affected by pre-test probability [1]. Some of these screening options include the Epworth Sleepiness Scale, the Berlin questionnaire, overnight oximetry,

and devices combining limited respiratory assessment, electrocardiogram (ECG), and oximetry. Specialized analysis of 24-h ECG recordings also has been proposed as a possible screening tool. The available screening options have many shortcomings, and so, patients in whom there is a high level of suspicion should be referred to a sleep specialist for over-night polysomnography [1].

Definitive evaluation for OSA is done by full-night, attended, diagnostic polysomnography with interpretation by a certified sleep specialist. Polysomnography usually includes airflow monitoring, respiratory effort, oxygen saturation using pulse oximetry, heart rate using a single-lead ECG, and for staging of sleep limited electroencephalogram (EEG), submental and tibial electromyograms (EMG), and bilateral electro-oculograms.

MECHANISMS OF OSA-INDUCED HYPERTENSION

Obstructive apneas may induce severe intermittent hypoxemia and CO₂ retention during sleep, with oxygen saturation sometimes dropping to $\leq 60\%$, disrupting the normal structured autonomic and hemodynamic responses to sleep [1, 7]. Apneas occur repetitively throughout the night and are accompanied by chemoreflex-mediated increases in sympathetic activity to peripheral blood vessels and consequent vasoconstriction and associated increases in blood pressure (BP) [8, 9]. Other contributing factors to OSA-related hypertension include systemic inflammation, oxidative stress, release of endogenous vasoactive factors, endothelial dysfunction and metabolic dysregulation [10, 11].

A growing body of evidence suggests that obesity and sleep apnea, in part via effects on BP and also via direct effects on the heart, may have long-term deleterious effects on cardiac structure and function [10]. Even after controlling for BP, OSA is an independent risk factor for the development of left ventricular hypertrophy, atrial enlargement, impaired right ventricular systolic and diastolic function, stroke, and death [12–15].

HYPERTENSION AND OSA

Both OSA and hypertension are common with many individuals having both conditions [1]. About 50% of OSA patients are hypertensive, and an estimated 30% of hypertensive patients also have OSA, often undiagnosed [16–19]. The Wisconsin Sleep Cohort Study described a linear relationship between 24-h BP and AHI that was independent of confounding factors such as body mass index (BMI) [20, 21]. In addition, analyses recently published found a significantly increased mortality risk in untreated sleep-disordered breathing patients, independent of age, sex, and BMI [22].

OSA is an independent risk factor for the development of hypertension because it precedes and predicts the onset of hypertension [1]. This has been demonstrated by the Wisconsin Sleep Cohort Study, which noted a consistent OSA–BP dose-response, even after controlling for age, sex, BMI, and antihypertensive medication use [16]. Normotensive subjects diagnosed with OSA at baseline had a significantly increased incidence of hypertension 4 years later compared with control subjects without OSA. The effects of OSA on hypertension may be most evident in middle-aged compared with older subjects, OSA tending to predominantly effect systolic BP [23].

OSA is particularly common in patients with resistant hypertension. In a prospective evaluation of patients with resistant hypertension (defined as a clinic BP of $\geq 140/90$ mmHg while taking a combination of ≥ 3 antihypertensive drugs), Logan *et al.* found that 83% of these patients had significant OSA with an AHI of ≥ 10 events/hr [24] (Figure 2.1). Particularly striking was that almost 100% of the men with resistant hypertension had OSA that up to that point had been unsuspected.

Excess aldosterone has been suggested as a possible mediator of the interaction between resistant hypertension and OSA [25, 26]. A study from our center provided evi-

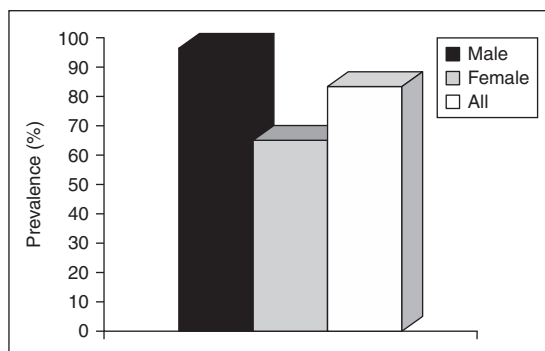


Figure 2.1 Prevalence of OSA in patients with resistant hypertension (modified from [24]).

dence of increased aldosterone excretion in resistant hypertensive patients with symptoms of OSA [25]. Following this, we showed that a significant correlation exists between plasma aldosterone concentration and severity of OSA in patients with resistant hypertension, but not normotensive control subjects [26]. Although we cannot directly infer causality from these studies, the results are consistent with the hypothesis that aldosterone excess may contribute to worsening severity of OSA, perhaps secondary to increased airway edema.

The clinical importance of recognizing that patients with resistant hypertension are at an increased risk of having both OSA and hyperaldosteronism is emphasized in the recently published AHA Scientific Statement on resistant hypertension [27]. In this statement it is highlighted that both OSA and primary aldosteronism are common and identifiable causes of resistance to antihypertensive treatment.

NOCTURNAL NON-DIPPING BLOOD PRESSURE PATTERNS

One of the characteristics of OSA-related hypertension is a non-dipping nocturnal BP profile [10]. This nocturnal hypertension is attributed, at least in part, to heightened sympathetic drive during sleep. Thus, the cumulative effect of excess sympathetic activation in sleep apnea patients, along with other vasoactive factors released in response to untreated OSA, contribute to both sustained daytime hypertension as well as nocturnal hypertension. However, even in the absence of daytime hypertension, sleep apnea patients may not exhibit the normal nocturnal dip in BP during sleep because of apnea-induced sympathetic activation.

OSA-induced nocturnal hypertension undoubtedly contributes importantly to the increased CV risk manifest in patients with OSA. As demonstrated by several recent studies of ambulatory blood pressure levels, including a long-term follow-up of nearly 4000 subjects, a blunted or the absence of a fall in nocturnal BP is strongly associated with increases in CV events and all-cause mortality [28].

SLEEP DURATION AND RISK OF HYPERTENSION

In patients with OSA, total sleep time is decreased secondary to frequent nocturnal arousals [10]. Recent observational data suggests that sleep duration is critically related to the risk of developing hypertension. For example, as observed in the First National Health and Nutrition Examination Survey, total sleep duration of <5 h per night was shown to significantly increase risk for developing hypertension in patients <60 years of age, even

after controlling for obesity and diabetes mellitus [29]. These findings are supported by results from the Sleep Heart Health Study, which suggest that sleep duration above or below a median of 7 to 8 h per night is associated with a higher prevalence of hypertension [30].

TREATMENT

Treatment of OSA includes, in general, weight loss, avoidance of alcohol, and CPAP [5]. Postural adjustments, such as not sleeping in the supine position, can provide benefit in patients with positional OSA, that is OSA that occurs mostly when sleeping in a certain position. Tracheostomy is considered a last resort in difficult-to-treat, medically complicated OSA. Whether any specific antihypertensive drug class offers superior BP control in patients with OSA is unclear [10].

CONTINUOUS POSITIVE AIRWAY PRESSURE

The mainstay of therapy for sleep apnea patients is CPAP, administered during sleep via a face or nasal mask [10]. Continuous positive airway pressure helps to maintain patency of the upper airway and usually enables complete or almost complete resolution of apnea [5]. Studies of short-term CPAP treatment on daytime BP control have been mixed, although the consensus seems to be that sustained, long-term treatment with CPAP can modestly reduce BP [31–33]. Continuous positive airway pressure has been shown to markedly and acutely decrease BP and sympathetic traffic during sleep [7]. Furthermore, CPAP may improve BP by mechanisms other than improving blood O₂ saturation, as suggested in a study comparing nocturnal supplemental oxygen therapy with CPAP [34].

The data regarding the antihypertensive effect of CPAP therapy, however, are not entirely consistent, with some studies demonstrating a large, consistently positive effect but with other studies not showing any antihypertensive benefit [35–37]. These studies demonstrated that while the overall benefit of CPAP on BP is modest, benefit on an individual basis can be substantial. In general, BP is reduced more in those patients with more severe OSA and with greater nightly CPAP use. Accordingly, CPAP should be attempted both to improve daytime symptoms of OSA and to lower BP, recognizing that the degree of benefit will be variable.

Recently, three meta-analyses of the effect of treating OSA with CPAP on BP have been published [1]. Overall, the net reduction in BP (approximately 1.5 to 2 mmHg) was significant but modest [38–40]. Thus, further studies are needed to evaluate the role of CPAP therapy and the effectiveness of different devices in treating OSA-associated hypertension. Given that OSA is so strongly associated with risk of developing hypertension, it may be that treatment of OSA will be most effective in preventing development or progression of hypertension, as opposed to actually lowering BP. Likewise, given the strong association between OSA and resistant hypertension, CPAP may be particularly beneficial in reducing the likelihood of developing resistance to antihypertensive therapies. Each of these possibilities needs testing by prospective studies.

EFFECT OF HYPERTENSION TREATMENT ON OSA

Different antihypertensive drug classes may have varying effects in patients with OSA, but there is little data comparing drug classes [1]. A comparison of the effects of five commonly used antihypertensive drugs (atenolol, amlodipine, enalapril, losartan, and hydrochlorothiazide) on BP and sleep architecture showed no effect on the severity of OSA [41]. Thus, there is presently no evidence that any specific antihypertensive drug attenuates sleep apnea severity [1].

TREATMENT OPTIONS IN OSA

Obesity is the single most important cause of OSA [1]. Weight loss can lead to a decrease in OSA severity, improved sleep efficiency, decreased snoring, and improved oxygenation. The most dramatic results have been reported with surgical weight loss [42].

Despite the effectiveness of CPAP in treating OSA, it is often not well tolerated, with up to 30% of patients stopping use within a few months after initiation of therapy [5]. Studies indicate that proper introduction of and education regarding CPAP, in both the sleep laboratory and the physician's office, are important in maintaining persistence with CPAP use [1].

CLINICAL PERSPECTIVES

OSA is convincingly linked to hypertension, both as an important mediator of cause and severity. Treatment of OSA acutely lowers BP, although the degree of benefit varies widely on an individual basis. Additional studies are needed to determine the long-term antihypertensive benefit of CPAP, and perhaps more importantly, the benefit of CPAP in preventing development and/or progression of hypertension. Observational studies indicate that treatment of OSA with CPAP decreases CV risk [10, 37]. The degree to which this risk is reduced secondary to lowering of BP versus other favorable effects remains to be determined [10].

CENTRAL SLEEP APNEA AND CONGESTIVE HEART FAILURE

Central sleep apnea (CSA) is characterized by repetitive cessation of ventilation during sleep resulting from loss of ventilatory drive [1]. That is, central apneas are distinguished from obstructive apneas, respectively, by a lack of respiratory effort compared with ongoing respiratory drive during upper airway obstruction. A central apnea is a ≥ 10 -second pause in airflow with no associated respiratory effort. Generally, >5 such events per hour are considered abnormal. Central sleep apnea syndrome is present when a patient has >5 central apneas per hour of sleep when associated with symptoms of disrupted sleep (frequent arousals) and/or daytime hypersomnolence [43]. Central apneas frequently occur in an individual with obstructive respiratory events (i.e. OSA). Although arbitrary, CSA is generally considered to be the predominant disorder if >50 – 80% of all events are central in etiology.

Central sleep apnea is much less common than OSA. Its etiology is often obscure, but the syndrome is associated with specific disorders with somewhat different underlying pathophysiologic mechanisms [1]. Cheyne-Stokes respiration most commonly occurs in patients with HF, although it has been described in association with neurological disorders, including neurovascular disorders and dementia. It is characterized by a crescendo–decrescendo pattern of breathing with a central apnea or hypopnea at the nadir of ventilatory effort [44].

Patients with HF and CSA may complain of paroxysmal nocturnal dyspnea and frequent nocturnal arousals and awakenings [1]; however, snoring, excessive daytime sleepiness, and obesity are less common than in patients with OSA. Significant CSA may be suspected by the clinician in high-risk patients such as those with advanced HF, but definitive diagnosis requires a full-night polysomnogram to determine the frequency and pattern of the central respiratory events.

Optimizing medical management of the HF can improve the severity of CSA. However, no randomized trials of treatment targeting CSA in HF patients have established a significant benefit with respect to hospitalization or mortality. Accordingly, there is no consensus as to when and how to treat CSA in the setting of HF. While the presence of significant central apneas predicts a negative outcome in patients with HF, it is unclear whether central apneas contribute independently to CV decline or instead are simply a marker of disease severity.

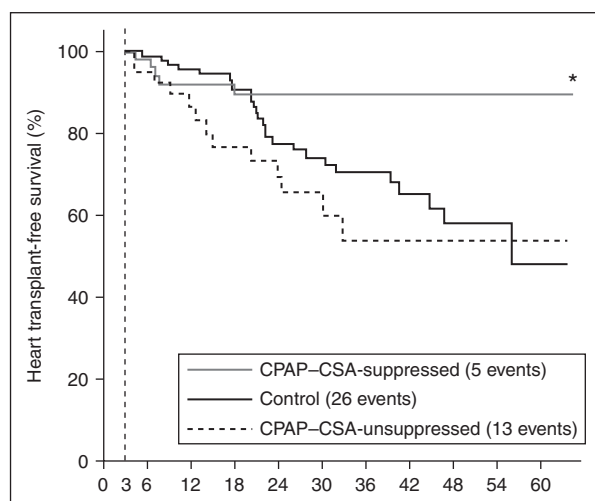


Figure 2.2 Kaplan-Meier survival plots demonstrates that subjects who had substantial suppression of their central apneas (CPAP-CSA-suppressed) had significantly improved heart transplant-free survival (*unadjusted $P = 0.043$), whereas the CPAP-CSA-unsuppressed group did not (unadjusted $P = 0.260$) (with permission from [46]).

In a multicenter, randomized trial involving 258 patients with systolic heart failure and CSA (the Canadian Positive Airway Pressure Trial for Patients With Congestive Heart Failure and Central Sleep Apnea or CANPAP), the use of positive airway pressure support at a standard level improved nocturnal O_2 saturation and caused a modest but significant improvement in ejection fraction [45]. However, in spite of these seemingly favorable effects, patients randomized to CPAP had no overall benefit compared with patients receiving sham treatment. After a mean follow-up period of 2 years, the primary outcome of combined mortality and cardiac transplantation was identical in the treated and control groups. Hospitalization rates also were unaffected by CPAP. In fact, the primary results of CANPAP suggested the possibility of early harm from CPAP use, with early divergence of transplantation-free survival favoring the control group ($P = 0.02$). Therefore, the use of CPAP in HF patients with CSA was not supported by the CANPAP results.

A *post hoc* analysis of the CANPAP results, however, indicated that if the analysis had been limited to patients who had substantial suppression of their central apneas (CPAP-CSA-suppressed), then benefit did occur in terms of increased left ventricular ejection fraction, and improved transplant-free survival at 3 months [46] (Figure 2.2). While such a retrospective analysis cannot be considered definitive, it does suggest that treatment of CSA with CPAP can be beneficial if it is effective in reducing the frequency of the central apneas. Prospective testing of such benefit is needed, however, before routine CPAP use can be recommended in this setting.

SUMMARY

In summary, at the present time, treatment of CSA is predicated upon optimizing medical treatment of the underlying HF. The long-term roles of supplemental oxygen and/or CPAP use to treat CSA in HF patients needs to be determined. While CSA is clearly associated with increased mortality in HF patients, it is unclear whether this represents a true cause and

effect or, instead, a marker of disease severity. This distinction is important clinically, as the former effect would suggest that effective suppression of CSA would reduce morbidity and mortality in these high-risk patients.

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Treatment of early morning surges in blood pressure

K. Kario

INTRODUCTION

There is a marked diurnal variation in the timing of cardiovascular (CV) events. Both clinically apparent and silent CV events occur most frequently in the morning hours [1]. Blood pressure (BP) exhibits a similar diurnal variation, with a surge occurring in the early morning hours. Although a rise in BP in the morning hours is a physiological phenomenon, the exaggerated nature of this rise (BP surge) may be pathologically relevant, independent of the average 24-h BP level [2–6].

An exaggerated morning BP surge is one of the components of various surges in BP, which occur in the ambulatory situation. The 24-h ambulatory BP variability includes various behavior-induced BP changes and specific components of diurnal BP variation, which are potential triggers for CV events in high-risk hypertensive patients. Blood pressure fluctuates the most during the morning hours. Consistent with this, the ambulatory BP reactivity index [7], the slope of the scatter plot of ambulatory BP against physical activity assessed by actigraphy, is highest in the morning [8].

Three issues are important when considering the importance of an exaggerated early morning BP surge: first, the morning BP surge can trigger acute CV events, which is most important in the high-risk hypertensive patient. In our previous prospective study in elderly patients with essential hypertension, an exaggerated morning BP surge emerged as an independent risk factor for clinical stroke [2]. Recently, three additional studies have also demonstrated that morning BP surge is a risk factor for both CV events and mortality independent of 24-h BP [9–11]. Second, the morning BP surge can potentiate target organ injury. The morning BP surge is associated both with hypertensive heart disease and with subclinical vascular diseases from small artery remodeling to instability of large artery atherosclerotic plaques [12]. Third, from an epidemiological standpoint, exaggerated morning BP surge may be one of the phenotypes for prehypertension (Figure 3.1) [13]. The morning BP surge could not only be the leading cause of vascular disease but also be a result of remodeling of small resistance arteries; thus, a cause and effect relationship. In the morning, vascular tone increases due to an overabundance of neurohumoral factors produced by both the sympathetic nervous system (SNS) and renin-angiotensin system (RAS). Ambulatory BP tends to increase earlier in the morning, compared with BPs during other periods of the day at the initiation stage of

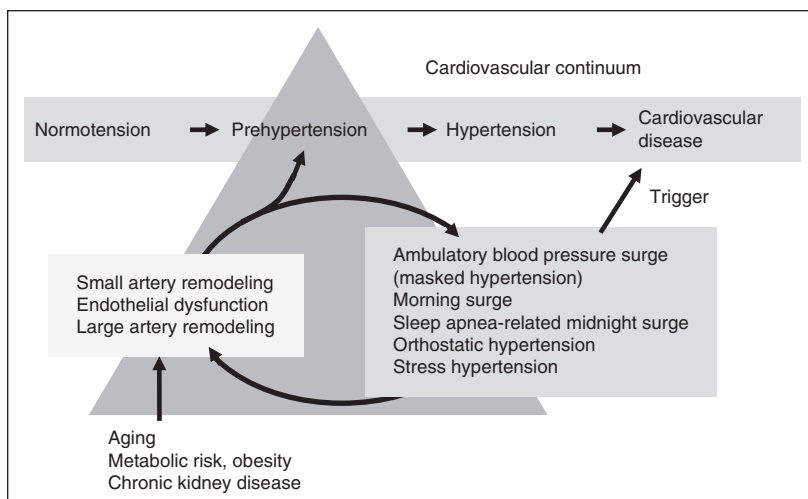


Figure 3.1 Exaggerated morning BP surge as a measure of prehypertension (hypothesis).

hypertension, after small artery remodeling is initiated [14]. Recent evidence indicates that high-risk hypertensive patients need continuous BP control throughout 24-h. The morning BP level offers insight into two features of the 24-h BP pattern – the extent of a morning BP surge and its contribution to the 24-h BP load. Clinically, antihypertensive medication targeting elevations in morning BP levels may provide more beneficial target organ protection and the capacity to prevent CV events, particularly in high-risk hypertensive patients [15].

IMPORTANT QUESTIONS

ARE THERE SPECIFIC RISKS ASSOCIATED WITH AN EARLY MORNING SURGE IN BLOOD PRESSURE?

There is growing evidence of the clinical implications of the morning BP surge on risk for CV events.

Cardiovascular events

Four recent prospective studies have demonstrated the possible risk of a morning BP surge for CV events [2, 9–11]. The first is our Jichi Medical School (JMS)-ambulatory blood pressure monitoring (ABPM) Study on elderly hypertensive patients. In the JMS-ABPM, a prospective study of 519 elderly hypertensive patients with a mean age of 72 years, a baseline 24-h ABPM was obtained together with brain magnetic resonance imaging (MRI) to assess for evidence of silent cerebrovascular disease [2]. The risk for stroke was studied during the follow-up period of 41 months. Both the sleep–trough surge (Figure 3.2), defined as the morning BP level (2-h-average) minus the lowest nocturnal BP, and waking surge, defined as the morning BP minus prewaking BP, were significantly associated with stroke risk independent of age, 24-h BP levels, and nocturnal BP dipping. For each 10 mmHg increase in baseline sleep–trough surge in systolic BP, the risk of stroke increased by 22% ($P = 0.008$).

A prospective study on 507 French patients with initially untreated hypertension also found similar results [9]. The hypertensive patients were classified into quartiles of the level

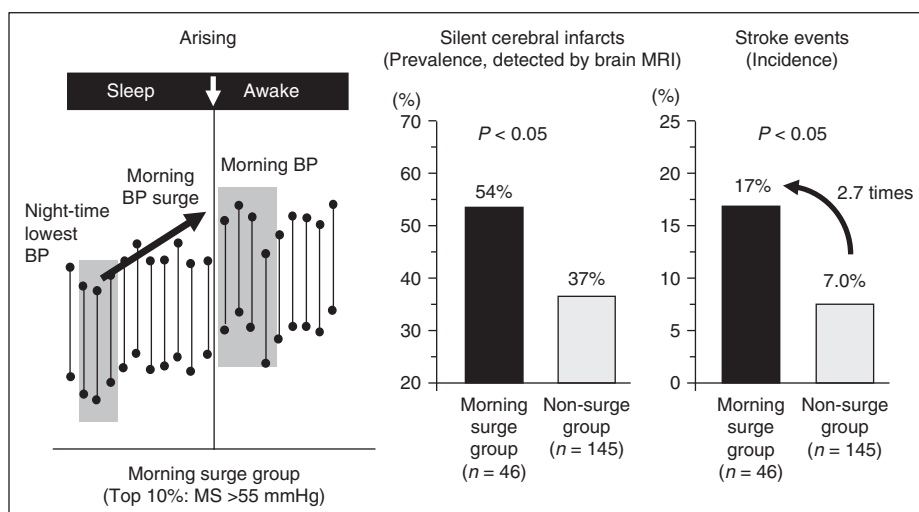


Figure 3.2 Morning BP surge and silent cerebral infarct and clinical stroke (JMS-ABPM Study) matching for age and 24-h systolic BP.

of waking surge, defined as morning systolic BP measured on standing minus systolic BP before rising. Although there were no significant difference in the 24-h BP levels between each group, during a 92-month mean follow-up, 23 CV events and 6 deaths occurred in the 253 patients with the highest morning BP surge, compared with eight events and no deaths in those with lower morning BP increases. In the multivariate analysis, the waking BP surge was significantly associated with CV risk independent of age and 24-h BP level. The Japanese population-based Ohasama study of 1430 people with a 10-year-follow-up period also confirmed that an exaggerated morning BP surge is an independent risk factor for hemorrhagic stroke ($P = 0.04$) [10]. In the Dublin Outcome Study [11], (11 291 patients, 5326 males, mean age 54.6), 566 CV deaths occurred during the 5.3-year-follow-period. This prospective study clearly confirmed the morning BP surge as a risk factor for both stroke and cardiac disease. The waking morning BP surge increased the risk for hard endpoints, both stroke and cardiac deaths, by approximately 40%.

Among the four studies above, only the JMS-ABPM investigated the association of the time of onset of events and an exaggerated morning BP surge, and demonstrated that the incidence of stroke occurring in the morning hours is higher in those with an exaggerated morning BP surge than in those without this degree of morning BP change [2].

Cardiovascular risk factors

Ambulatory BP variability including morning BP surges are more exaggerated in hypertensive patients than in normotensive patients [2, 16]. Advancing age also increases BP variability. In fact, both increasing age and 24-h BP levels are significant determinants of exaggerated morning BP surges [2].

Progress in understanding the mechanisms of the morning BP surge in hypertensives and its risks are a basis for placing more attention on treatment strategies that will ensure anti-hypertensive efficacy during this vulnerable period. Many mechanisms are interrelated, producing the potential for a vicious cycle of heightened hyperreactivity and increased vascular disease progression. However, the central mediator is an activated SNS, including upregulation of the RAS, which drives vasoconstriction and increases BP [12]. This results

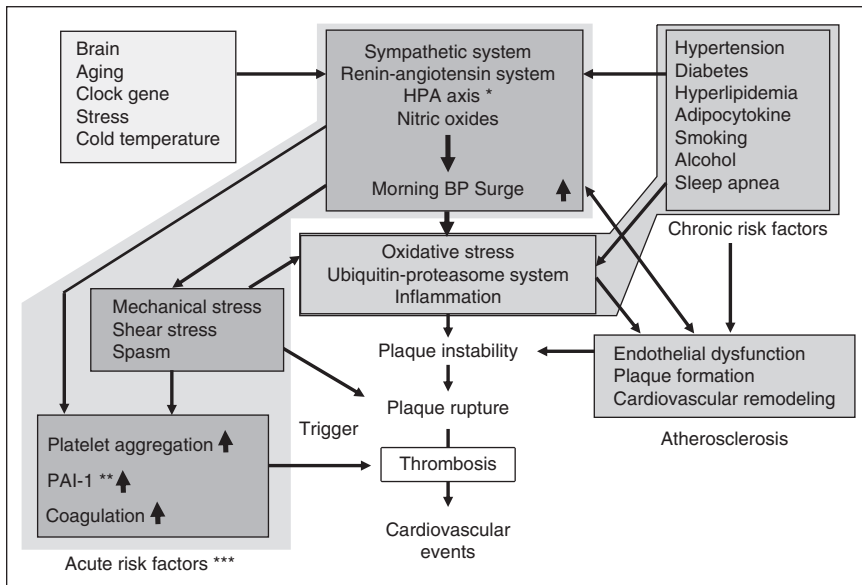


Figure 3.3 Morning blood pressure surge: related cardiovascular risk.

* hypothalamic-pituitary-adrenal axis; ** plasminogen activator inhibitor-1;

*** with diurnal variation.

in increased mechanical stresses on the vascular wall, endothelial dysfunction, and oxidative stress [17, 18], setting the stage for downstream pathophysiologic responses that include release of proinflammatory factors, such as C-reactive peptide (CRP), release of prothrombotic factors, such as plasminogen activator inhibitor (PAI-1), and proliferative factors that contribute to cardiac and vascular remodeling (Figure 3.3) [12].

DOES EARLY MORNING BLOOD PRESSURE HAVE ANY RELATIONSHIP TO SURROGATE MARKERS OF END-ORGAN DISEASE SUCH AS MICROALBUMINURIA?

There are compelling data demonstrating a significant association between morning BP surge and various surrogate markers of target organ damage from the early to end-stages, independent of 24-h BP level.

Silent cerebrovascular disease

Silent cerebral infarcts are the strongest surrogate markers of future clinical strokes, particularly in the setting of an increased atherosclerotic inflammatory reaction [19, 20]. In the JMS-ABPM Study, silent cerebral infarcts detected by brain MRI, particularly multiple silent cerebral infarcts, were more frequently detected in the morning surge group than in the non-surge group (Figure 3.2) [2]. Silent cerebral infarcts are usually lacunar infarcts having occurred in small cerebral arteries. It is well known that sympathetic activity, particularly α -adrenergic activity, is increased in the morning, in our study silent cerebral infarcts were more closely associated with the component of the morning BP surge attributable to α -adrenergic activity (as defined by the reduction of morning BP surge by night-time administration of the α -blocker, doxazosin [maximal dose of 8-mg]) than to the overall morning BP surge [21].

Left ventricular hypertrophy

An exaggerated morning BP surge also appears to increase the likelihood of hypertensive heart disease. The morning BP surge increases cardiac afterload and arterial stiffness, contributing to the progression of vascular disease. In our community-dwelling subjects, the morning BP surge adjusted for morning physical activity was significantly correlated with left ventricular mass index, as assessed by echocardiography [22], as found in a French study [9]. Higher morning BP minus evening BP (ME-difference) values, assessed by self-measured BP monitoring is also an independent determinant of increased left ventricular mass in both untreated and treated hypertensive patients [23, 24]. In addition, those hypertensive patients with a morning BP surge (defined as a rise in systolic BP ≥ 50 mmHg and/or diastolic BP ≥ 22 mmHg during the early morning (6:00 to 10:00 AM) compared with mean BP during the night) had a prolonged QTc duration and greater QTc dispersion in the morning period compared with those without such a morning BP surge [25]. The prolongation of cardiac repolarization times and morning sympathetic overactivity that align in hypertensive patients with morning BP peaks, may be one factor that contributes to the raised CV risk in these patients.

Microalbuminuria

Patients with chronic kidney disease (CKD) not uncommonly exhibit a non-dipping nocturnal BP pattern [26, 27] and this non-dipping pattern might precede the development of microalbuminuria [28]. One cross-sectional study in 31 normotensive patients with newly-diagnosed type 2 diabetic demonstrated that morning BP levels and morning BP surges were significantly increased in patients with microalbuminuria compared with patients without microalbuminuria even when corrected for age, sex, and duration of diabetes [29]. This suggests that the systemic BP surge might directly induce a significant rise in intraglomerular pressure in the setting of disrupted autoregulation in glomerular afferent arterioles. In another study of type 2 diabetic patients, those with morning BP hypertension (morning BP level measured at home $>130/85$ mmHg) had increased frequencies of diabetic renal disease, retinopathy, microvascular disease and vascular complications, including coronary artery disease and cerebrovascular disease [30]. In this study, hypertension defined by BP levels measured in the clinic setting was not associated with these same complications.

Carotid atherosclerosis

Morning surges in BP may facilitate progression of carotid atherosclerosis and induce plaque instability through heightened inflammation. Recently, untreated hypertensive patients with a morning BP surge were reported to have increased carotid intima-medial thickness and higher levels of inflammatory markers such as interleukin 6 and CRP, than those without a morning BP surge [31]. Another recent study also demonstrated that an increased rate of SBP variation during the morning BP surge was independently associated with increased carotid intima-medial thickness in untreated hypertensive patients [32].

In addition, a more recent study investigated the association of morning BP surge and carotid plaque characteristics in hypertensive patients with carotid artery stenosis [18]. In this study, plaques obtained by carotid atherectomy in those with an exaggerated morning BP surge were more likely to be vulnerable plaques (higher numbers of macrophages and T-lymphocytes, and increased expression of HLA-DR antigen), to have increased markers of oxidative stress, and to exhibit activation of the ubiquitin-proteasome system and nuclear factor kappa B (NF- κ B, a transcriptional factor regulating a large number of genes involved in inflammation). With higher levels of matrix metalloproteinase-9 (MMP-9), the most important enzyme modulating risk for acute plaque rupture, this study suggests that exaggerated morning BP surges are associated with atherosclerotic plaque instability.

Small artery disease

Small artery remodeling is significantly correlated with morning BP surges in essential hypertension. In one recent study, small artery remodeling was directly assessed by the media thickness to lumen diameter ratio (M/L ratio) of subcutaneous small arteries [33], indicating another important role of the morning BP surge in the etiology of hypertension. In addition to being a consequence of hypertension, small artery remodeling is also important as a leading cause of hypertension, which ultimately is a disease of increased peripheral resistance. [14]. Various neurohumoral factors, including both the SNS and the RAS, are activated in the morning hours. The morning surge triggered by these pressor systems could be augmented in the presence of small artery remodeling, because of a limited capacity for vasodilation [13].

Increased sympathetic activity, particularly α -adrenergic stimulation, increases vascular tone in small resistance arteries and may contribute to the morning BP surge. In fact, the bedtime dosing of an alpha-adrenergic blocker preferentially reduces morning BP levels and morning BP surges, particularly in those with silent cerebral infarcts (small artery disease) [21].

Endothelial dysfunction

In the morning, endothelial cell dysfunction is found even in healthy subjects, and this may contribute to the morning BP surge secondary to small artery remodeling [34]. Thus, the threshold for the BP surge by pressor stimulation may be the lowest in the morning. The morning hours appear to be a sensitive period for detecting surges and variability in BP, which likely reflect altered vascular tone and structure.

WHAT ARE THE BEST THERAPIES TO TREAT EARLY MORNING RISES IN BLOOD PRESSURE?

Treating patients with an antihypertensive medication targeting morning hypertension based on self-measured BP monitoring is the first step toward achieving strict BP control throughout the 24-h period [3, 15]. Current evidence suggests that the majority of patients medicated on the basis of clinic BP are not achieving adequate control during this vulnerable period [3]. Sixty percent or more of medicated hypertensive patients do not achieve the target BP level of <135/85 mmHg in the morning [35]. Although there are no definitive outcome data relating a specific reduction in early-morning BP to declines in early-morning CV events, there are consistent findings that relate the impact of uncontrolled early-morning hypertension and clinical outcomes.

Choosing drugs with longer half-lives

Medications for preventing morning surges in BP include long-acting calcium channel blockers (CCBs), such as amlodipine, and thiazide-type diuretics amongst others; the longer acting the antihypertensive, the better it is for controlling morning BP. Such long-acting drugs are typically administered once daily in the morning and, in theory, provide continuous BP reduction over a 24-h period to attenuate morning BP surges.

Antihypertensives that maintain pharmacodynamic effects into the early-morning period are likely to have a superior effect on the early-morning BP surge. In 76 patients with hypertension treated once daily in the morning with the angiotensin-receptor blocker (ARB) valsartan 40–160 mg (mean dose: 124 mg/day) or the CCB amlodipine 2.5–10 mg (mean dose: 6.4 mg/day), the two agents were similarly effective in reducing clinic and 24-h mean BP. However, the mean change from baseline in the early-morning BP was -6.1 mmHg for amlodipine, compared with $+4.5$ mmHg for valsartan ($P < 0.02$) [36]. The most readily apparent explanation for the observed treatment difference is the pharmacokinetic profiles of the two agents: the half-life of amlodipine (about 34 h) is

substantially longer than that of valsartan (about 9 h). Similarly, among the angiotensin-converting enzyme inhibitors (ACE-I), longer-acting agents, such as trandolapril [37], appear to reduce the early-morning BP more effectively than shorter-acting ones, such as ramipril [38]. Chronopharmacological formulations taken at bedtime, such as controlled-onset extended-release verapamil, have also been shown to reduce the early-morning BP surge quite effectively without an undue reduction in BP during the night-time hours [39].

Diuretics provide the longest duration of BP lowering effect and their effectiveness for the prevention of CV events is well established. However, when morning hypertension is treated using diuretics, night-time BP levels are predominantly reduced compared with daytime BP, and 'non-dippers' shift towards becoming 'dippers' [40]. A greater nocturnal fall of BP by diuretics may lead to a larger morning surge of BP. The reduction of nocturnal BP is greater with the combination of RAS inhibitors and diuretics than amlodipine therapy under conditions of comparable BP lowering during the daytime hours [41]. This characteristic (greater night-time BP reduction) of ambulatory BP lowering by diuretics may partly account for the recent results of The Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension (ACCOMPLISH) trial [42], which showed that combination therapy with an ACE-I and a CCB (benazepril and amlodipine) was superior to the combination of an ACE-I and a diuretic (benazepril and hydrochlorothiazide) for CV protection in high-risk patients with hypertension, even when the control of systolic BP was well achieved in both combination arms (reaching levels around 130 mmHg systolic).

Sympathetic inhibitors

More specific treatment for morning BP surges may be achieved using antihypertensive medications that reduce the pressor effect of those neurohumoral factors more active in the morning hours, such as inhibitors of sympathetic activity or the RAS.

Alpha- and α/β -blockers are effective in reducing the morning BP surge in hypertensive patients. In particular, bedtime dosing provides the best BP lowering effect in the morning. Morning BP and the morning BP surge in hypertensive patients are effectively reduced with bedtime dosing of doxazosin, when compared with ambulatory BP over other time periods during the 24-h of dosing effect [21]. In addition, as noted previously, the α -adrenergic component of the morning BP surge is closely associated with the number of silent cerebral infarcts (10 mmHg BP increase: OR = 1.96; $P = 0.006$), independent of age, the overall morning BP surge, 24-h systolic BP and a range of other cofactors. In addition, the Japan Morning Surge-1 (JMS-1) study demonstrated that bedtime dosing of doxazosin significantly reduces morning BP and urinary albumin excretion ratio (UAR) in medicated patients with morning hypertension [43], who were receiving at least one antihypertensive drug. In this study, while the UAR decreased in parallel with the reduction in morning BP, the absolute reduction in the UAR was, to a degree, independent of the reduction in morning BP.

Although there is no evidence that β -blockers reduce the morning BP surge, carvedilol, a β -blocker with partial α -adrenergic inhibitory activity, may be effective. In one study, 128 patients with an elevated early-morning BP were randomized to once-nightly therapy with either the selective β_1 -blocker metoprolol 100–200 mg or the non-selective α/β -blocker carvedilol 12.5–25 mg [31]. After 12 months, a greater decrease in early-morning BP occurred with carvedilol (27.3 *vs* 20.2 mmHg; $P = 0.001$). Moreover, a higher proportion of patients treated with carvedilol displayed net regression of carotid atherosclerosis (49% *vs* 18%; $P < 0.01$).

Thus, the bedtime dosing of a sympatholytic agent, particularly one with α -adrenergic inhibitory activity, can be of some particular utility in the specific management of morning hypertension and in so doing may confer target organ protection.

RAS inhibitors

The RAS is activated in the morning and could contribute to the morning BP surge and the increase in CV risk during that time period. A recent report demonstrated that a vaccine targeting angiotensin II significantly reduced BP throughout a 24-h period with the observed BP reduction being most prominent during the morning hours [44]. The time-wise nature of this BP reduction indicates that both the RAS and its related pressor effects are decidedly activated in the morning hours.

Recently, it has been demonstrated that tissue RAS activity also exhibits diurnal variation, possibly regulated by a 'clock gene'. In addition to the reduction of the morning BP level owing to RAS activation, the morning activation of the tissue RAS could be suppressed, leading to increased protection against hypertensive target organ damage and CV events in hypertensive patients. However, different ARBs and ACE-Is have differing effects on morning BP levels and morning BP surges. The BP lowering effect of ARBs on morning BP levels and morning BP surges is dependent on differences in plasma half-life and the characteristics of binding to and dissociation from the vascular angiotensin II type 1 receptor.

For example, one double-blind, randomized trial compared the effect of the ARB telmisartan (40–80 mg once daily), which has the longest plasma half-life (24 h) and valsartan (80–160 mg once daily), which has an intermediate half-life (6–9 h), on early morning BP in 490 patients with hypertension [45]. Ambulatory BP recordings were performed at baseline after a placebo period and again after 6 and 8 weeks of double-blind therapy in a randomized crossover design. After the active dose, telmisartan reduced the BP during the last 6 h of the dosing period by $-11 \pm 0.8 / -7.6 \pm 0.6$ mmHg compared with $-8.7 \pm 0.8 / -5.8 \pm 0.6$ mmHg for patients on valsartan ($P = 0.02$ for systolic BP and $P = 0.01$ for diastolic BP), indicating that telmisartan achieved a greater effect than valsartan on BP during the early morning period in patients with hypertension.

Evaluation of the effect of RAS blocking agents on early-morning BP has been evaluated in a pooled analysis of two prospective, randomized, open-label, blinded-endpoint trials comparing the ARB telmisartan (80 mg) and the ACE-I ramipril (10 mg) [46]. In 1383 patients meeting inclusion criteria for the pooled analysis of early-morning BP surge, the mean change from baseline to endpoint in morning systolic BP surge was -1.5 (SE, 0.47) mmHg for telmisartan and $+0.3$ (0.47) mmHg for ramipril ($P = 0.0049$). Of interest, in patients with a baseline morning BP surge in the highest quartile, the changes in systolic early morning BP surge were -12.7 (0.91) mmHg for telmisartan, compared with -7.8 (1.02) mmHg for ramipril ($P = 0.0004$).

Candesartan has a similar elimination half-life; however, its tissue-based half-life and affinity appear stronger than valsartan. A prospective crossover study was performed in 73 essential hypertensive patients to compare the effects of candesartan and lisinopril on ambulatory BP and early-morning BP [47]. Twenty-four-hour ABPM was performed at baseline and for each active treatment. Small doses of a thiazide diuretic were added as needed. The effects of both drugs on 24-h BP were almost identical and satisfactory. Patients were classified into a morning surge group (the highest quartile of morning systolic BP surge >36 mmHg) and a non-morning surge group (the remaining three quartiles of morning BP surge). Candesartan was superior in decreasing morning BP and morning BP surge.

IS A CHRONOPHARMACOLOGICALLY ADMINISTERED MEDICATION GIVEN AT BEDTIME THE PREFERRED THERAPY FOR EARLY MORNING BLOOD PRESSURE CONTROL?

The most effective time for administering an antihypertensive drug for controlling morning hypertension is at bedtime. This approach is effective not only for reducing morning BP but also for reducing 24-h BP and target organ damage.

Whether antihypertensive agents are dosed once in the morning or twice daily, the trough drug level occurs in the morning hours just prior to the next dose. If trough levels do not

provide adequate antihypertensive activity, the loss of BP control is associated with a period of exceptional vulnerability for both acute events and activities that drive chronic disease progression. Thus, morning BP levels should be measured using self-measured BP monitoring in all medicated hypertensive patients. To achieve morning BP levels <135/85mmHg, self-measured morning BP-guided by chronopharmacologically administered therapy at bedtime should be considered.

Calcium channel blockers

A recent trial investigated the administration-time dependent antihypertensive efficacy of the slow-release, once-a-day nifedipine gastrointestinal-therapeutic-system (GITS) formulation in 180 untreated hypertensives (86 men and 94 women) [48], randomly assigned to receive nifedipine (30 mg/day) as a monotherapy either upon awakening or at bedtime. After 8 weeks of treatment, the BP reduction after treatment was significantly larger with bedtime dosing mainly during night-time sleep ($P < 0.012$), and the morning surge of BP, a risk factor for stroke, was significantly reduced ($P < 0.001$) but only after bedtime administration of nifedipine. The increased efficacy on ambulatory BP as well as the significantly reduced prevalence of edema after bedtime as compared with the morning ingestion of nifedipine should be taken into account when prescribing this medication, as well as other CCBs to patients with essential hypertension.

Sympathetic inhibitors

All the evidence of a beneficial effect on controlling morning hypertension, described above, are typically achieved by bedtime-dosing. Thus, when we use the sympathetic inhibitors as the antihypertensive therapy for controlling morning hypertension in addition to other drugs, we should opt for bedtime dosing.

RAS inhibitor

Bedtime-dosing of RAS axis inhibitors would be more effective for controlling morning hypertension and possibly preventing target organ damage [49]. In a study using telmisartan, 215 patients with hypertension (114 men and 101 women) were randomly assigned to receive telmisartan (80 mg/d) as a monotherapy either on awakening or at bedtime. After 12 weeks of treatment, telmisartan administered at bedtime, as opposed to morning dosing, improved the sleep time-relative BP decline toward more of a 'dipper' pattern without loss in 24-h efficacy [50]. However, the beneficial effect of bedtime dosing of RAS inhibitors may not be attributable to reducing morning BP surges, but rather to reducing night-time BP during the hours of sleep [51]. In this study, there was no significant difference in the reduction of morning BP surge between the two groups [50].

HOW TO MANAGE HIGH-RISK MORNING HYPERTENSION

Considering that an exaggerated morning BP surge is related to plaque instability in hypertensive patients with carotid stenosis (and probably other locations as well) [31], controlling morning BP surge in this vulnerable period would be important for preventing CV events, through stabilizing plaques and reducing the mechanical stress associated with acute plaque rupture in high-risk patients.

The morning BP surge-dependent increase in shear stress and the increased pressure on vascular walls increases oxidative stress, while inducing the activation of the ubiquitin-proteasome system, thereby causing an inflammatory reaction through the activation of NF- κ B as described above [31]. These activations are also known to be closely affected by tissue RAS activity. Therefore, antihypertensive therapy targeting angiotensin II suggests that complete 24-h RAS inhibition may, therefore, be a promising modality for more effective

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Use of out-of-office blood pressure monitoring versus office-based measurements for managing patients with hypertension

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SUMMARY

In the management of patients with hypertension, blood pressure (BP) has been traditionally measured in the physician's office. However, over the past two decades, technological advances have provided useful options for measuring BP with home and ambulatory BP monitoring. These methods are gaining wider acceptance in clinical practice as cardiovascular outcome data have been published and as clinicians recognize the comprehensive nature of the information derived from out-of-office BP measurements. Self (home) BP measurements also help to empower patients and involve them more responsibly in their own care. In this chapter we discuss the advantages and limitations of the various methods of BP measurements and the devices available for out-of-office BP monitoring as well as their use as clinical tools for management of patients with hypertension.

OFFICE BLOOD PRESSURE MEASUREMENT: BENEFITS AND PITFALLS

Measurement of blood pressure (BP) in the physician's office has been the traditional method for diagnosing and monitoring BP in hypertensive patients. It has also been the methodology used in many major cardiovascular outcome trials and has the advantage of being done by trained personnel using validated instruments. If done properly, office BP measurement has substantial clinical value; however, in today's *rushed* practice of medicine, this may not always be the case. Repeated measurements over a period of several minutes in the examination room are the exception rather than the rule. Thus, a "white-coat effect" (an increase in BP only in the medical care environment) is reported often — in as many as 20 to 35 percent of patients in whom hypertension is diagnosed [1].

Improper training of medical staff and observer error such as terminal digit preference and single number preference can also lead to inaccuracies in measurement. Terminal digit preference is the tendency to round off readings to a particular number, (usually zero) and

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Table 4.1 Recommended cuff/bladder widths based on mid-arm circumference to avoid miscuffing (derived with permission from the American Heart Association [5])

Arm circumference (cm)	Recommended cuff bladder size	
22–26	Small adult	12 x 22 cm
27–34	Adult	16 x 30 cm
35–44	Large adult	16 x 36 cm
45–52	Adult thigh	16 x 42 cm

thereby lead to over- or underestimation of actual BP. This digit bias can lead to misdiagnosis and inaccurate assessment of the adequacy of antihypertensive treatment. In a study of 28 841 pregnant women [2], 78% of prenatal BP readings were found to have a terminal digit preference of zero. Furthermore, when the threshold for hypertension was changed from ≥ 140 to > 141 mmHg, the authors found a reduction in the prevalence of hypertension from 25.9 to 13.3% [2].

As mercury and aneroid sphygmomanometers are calibrated in increments of 2 mmHg, the terminal digits of both systolic and diastolic BP measurements should only be 0, 2, 4, 6 or 8. Studies have demonstrated increased preference for certain terminal digits influenced by observer bias, previous patient readings or preset cut-offs [3, 4]. This problem can also affect the validity of data in clinical trials. In the Syst-Eur trial where the goal systolic BP was < 150 mmHg, there was increased frequency of systolic BPs of 148 mmHg [4]. In addition, 42% of the initial seated systolic BP readings ended in zero. However, with monitoring, retraining and feedback to the clinical study sites, this phenomenon was reduced to 20 to 30% during the trial [4]. The problem of digit bias is encountered to a lesser extent in specialty hypertension practices [3] due in part to an increased focus on proper measurement techniques and the methodology of obtaining the BP readings [3].

The American Heart Association recommendations for BP measurement provide guidelines for the correct technique of measuring BP in the office setting [5]. At the initial visit, BP should be measured in both arms. The patient should be instructed to relax as much as possible and to not talk during the measurement procedure; ideally, 5 minutes should elapse before the first set of readings are taken. The individual should be comfortably seated, with the legs uncrossed, and the back and arm supported, such that the middle of the cuff on the upper arm is at the level of the right atrium (the mid-point of the sternum). An appropriate cuff and bladder size should be selected, as a bladder that is too small relative to the patient's arm circumference will give erroneously high readings [6]. The "ideal" cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference (a length-to-width ratio of 2:1). However, 'miscuffing' (the use of an undersized or oversized cuff) remains a relatively common problem leading to inaccurate BP assessment and diagnosis which may result in over- or undertreatment in many cases [7] (Table 4.1).

Attention should be given to the proper placement of the cuff and stethoscope, and appropriate rate of inflation and deflation (2–3 mmHg/ sec). The observer should recognize subject and environmental factors that can affect BP such as room temperature, recent exercise, smoking, talking, arm position, and muscle tension.

Another potential source of error can be the auscultatory gap, which is a phenomenon in older patients with a wide pulse pressure when the Korotkoff sounds may become inaudible between systolic and diastolic pressure, and re-appear as cuff deflation is continued.

Even when proper technique is followed conscientiously, BP measurements in the doctor's office provide only a small number of readings and there are often large variations in the BP values measured in the clinic within a single visit and among several visits. The pres-

ence of white coat hypertension, white coat effect and masked hypertension also creates the concern that the office BP measurements aren't reflective of the individual patient's *true* BP values.

Some of the technical and artifactual problems mentioned above can be overcome by using automated oscillometric devices that have the ability to take multiple BP measurements [8, 9]. Though observer input is still required for proper cuff selection and placement and for patient positioning, these devices can significantly decrease observer bias and may dissipate the white coat effect in the clinical environment, when taken with the patient resting quietly and alone. Recent studies have shown that automated office BP readings are typically lower than observer-measured office BP and also correlate better with the 24-h BP, a better predictor of future cardiovascular events [8, 9]. The quality of automated office BP monitors have improved substantially in recent years and are being more widely used in clinical studies and practices. It is expected that these devices will replace mercury column sphygmomanometers and even aneroid devices as they improve in precision and cost.

Given the many shortcomings of BP measurements in the clinical environment and also the added information gained through ambulatory and self-BP measurements, the utility of out-of-office monitoring to supplement clinic BP values has increased markedly.

OUT-OF-OFFICE BLOOD PRESSURE MONITORING

Out-of-office monitoring of BP includes both self-BP measurements by patients and automated ambulatory BP recordings obtained by physician's offices; these techniques have become more popular among patients and are being recommended more routinely by practicing physicians. Though not mandatory for the diagnosis of hypertension in all patients with elevated BPs in the medical care environment, both self- and ambulatory BP serve as useful adjuncts to BP measurements obtained in office. Out-of-office BP monitoring can enhance the ability to identify white-coat and masked hypertension as well as to evaluate BP control in patients on complex antihypertensive drug regimens.

SELF (INCLUDING HOME) BLOOD PRESSURE MONITORING

Self-BP monitoring refers to measurements by the patient or a caregiver at their home, place of employment or a neutral environment such as a neighbor's home, pharmacy, assisted living or exercise facility. Self-BP monitoring (SBPM) has the advantage of providing a large number of readings obtained in an environment where patients spend the majority of their time and theoretically are more representative of their average daily pressure. The use of SBPM has been recommended by several guideline committees for the management of hypertension, including the European Society of Hypertension (ESH) [10, 11], the American Society of Hypertension (ASH) [12], the American Heart Association [5], the British Hypertension Society [13], the Japanese Hypertension Society (JHS) [14], the World Health Organization-International Society of Hypertension [15] and JNC 7[16].

Self-BP monitoring is relatively inexpensive for patients though still rarely covered by third party payors. The availability of several new, user-friendly semi-automatic oscillometric devices has made SBPM feasible for a larger number of patients. Numerous studies have demonstrated that home/self-measurements of BP are more reproducible than office BP measurements, both in short-term and long-term comparisons [17, 18]. This finding is due in part to the lower BP variability seen with SBPM. Self-measured BP also correlates better with hypertensive end organ damage such as left ventricular hypertrophy, albuminuria and carotid intima-medial thickness [19, 20]. Home BP readings also have demonstrated significant prognostic value. Recent prospective studies have shown that elevated home BP predicts future cardiovascular events better than clinic BP [21–23] and more closely relates with cardiovascular mortality, stroke incidence and progression to end-stage renal disease. The

Ohasama study was a population based study from Japan comparing home and office BPs in 1789 subjects followed for a mean duration of 6.6 years [21]. The subjects measured home BPs within 1 h of waking over a 4-week period and office BPs were taken during annual health check-ups. In the Ohasama study cardiovascular mortality was shown to have a stronger association with home BP values than office BPs [21]. Subsequent analysis of the data also showed that home BP values better predicted the risk for future hemorrhagic or ischemic stroke [24].

The Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study is another recent study that compared the prognostic value of office, home and ambulatory BP monitoring in an Italian population [22]. All three measures of BP were directly related to cardiovascular mortality. However, for the same numeric increment, cardiovascular mortality increased most steeply with a rise in ambulatory BP followed by home and then office BP [22].

One of the major advantages of self-BP monitoring is the improved ability to identify white-coat hypertension, defined as an elevated BP occurring only in the medical care setting and seen in as many as 20 to 35 percent of patients in whom BP is elevated in the clinical setting. White-coat hypertension is more common in the elderly and has a better prognosis than that for patients with sustained hypertension outside of the clinical environment. Since self/home BP values are more representative of the patients' true BP, it has been suggested to be a better means to assess and follow BP control in patients on antihypertensive therapy. Furthermore, SBPM may be useful in preventing use of unnecessary antihypertensive therapies in patients with white-coat effect and thereby avoid the consequences of excessive dosing. In the Treatment of Hypertension Based on Home or Office Blood Pressure (THOP) Trial the investigators adjusted antihypertensive drug therapy in a step-wise manner based on home or office diastolic BPs [25]. Patients in the home BP group had less intensive drug treatment and marginally lower costs. BP control was similar up to 6 months, however, on follow-up at 1 year; patients in the office BP group had significantly larger changes in BP [25]. This trial demonstrated the benefit of self/home BP monitoring in lessening treatment intensity but also highlighted that office monitoring plays an important role in maintaining long term BP goals.

In contrast, masked hypertension, also known as 'hidden hypertension' or 'reverse white-coat effect', is the presence of elevated BP values outside of the medical care environment with normal in-clinic BP levels; this syndrome may be present in as many as 10% of normotensive or prehypertensive patients [26]. Out-of-office BP measurements may be used to identify and follow patients with masked hypertension. Given the advantages of SBPM, the two main indications for its use in clinical practice include the assessment of white-coat hypertension and monitoring of effective BP control in conjunction with office measurements. Self-BP monitoring can thus overcome a number of shortcomings of office BP measurement. It can be incorporated into the routine care of hypertensive patients and like glucose monitoring for diabetics can help empower patients, improve compliance and lead to better overall BP control (27, 28).

Discrepancies between office and self/home BP should be taken seriously and evaluated further with ambulatory BP monitoring if clinically appropriate (Figure 4.1).

Limitations of self-BP monitoring

Self- and home BP monitoring also have limitations. Self-BP measurements may be inaccurately performed and reporting bias may be present as patients may not present the totality of their readings. These shortcomings can be avoided to some extent by educating patients in the proper technique of self-BP measurement and by the use of automated devices with display screens and/or in some cases with memory, which can keep a record of several readings and thus eliminate reporting bias. Though home BP is usually taken in a relatively

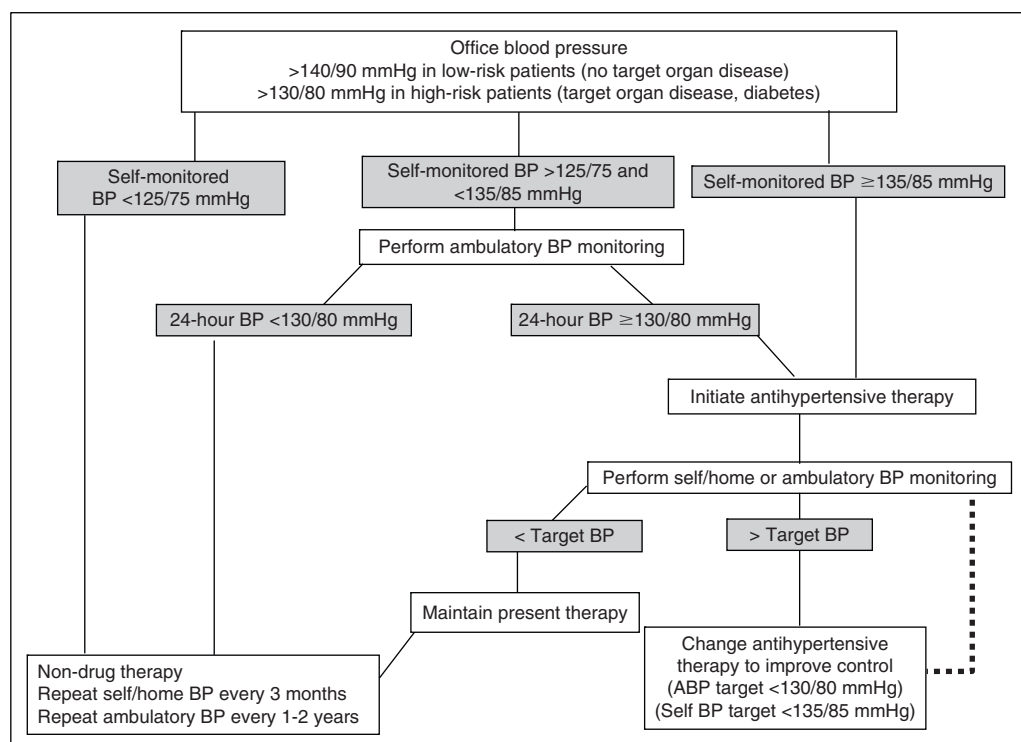


Figure 4.1 Algorithm for the use of self/home BP monitoring and ABPM in clinical practice (with permission from the ASH Position Paper [36]).

relaxed setting, it can lead to anxiety in some individuals, who need to self-report their BP or who might become overly 'obsessed' with their BP control. Unlike ambulatory BP monitoring, SBPM can not measure BP during sleep (although future SBPM devices may develop this capacity).

To ensure reliability of the data from SBPM it is essential that properly calibrated and validated devices are used. As outlined in the next section, independent validation is an extensive process and many of the devices currently available in the marketplace do not meet the recommended standards.

Validation of automated BP monitoring devices

Most present-day self (or home) BP monitors are semi- or fully-automatic with liquid crystal display (LCD) screens and use oscillometric technology to obtain BP values. Oscillometry detects initial and maximal arterial pressure oscillations and uses set algorithms to calculate the systolic, mean, and diastolic BP. Newer technology has improved the validity and reliability of many automated BP monitors developed for self-measurement [28–30]. Furthermore, these automated oscillometric devices provide values which predict 24-h BP and target organ damage, comparably if not better than BP measurements obtained via auscultatory method in a clinic setting [28–30]. It is essential that SBPM be validated for accuracy and reliability before they are used in clinical research and practice. Independent

validation procedures are rigorous and not all devices available in the market meet these criteria [31–35].

There are three key, published protocols that have been recognized to determine the accuracy and reliability of non-invasive blood pressure monitors. These include the Association for the Advancement of Medical Instrumentation (AAMI) [31], BHS [35], and the ESH [32]. These protocols describe the requirements for clinical testing, labeling, safety, and performance of non-invasive BP monitors, encompassing ambulatory BP monitors. The AAMI described the first protocol in 1987 with subsequent revisions in 1992 and 2002. The most recent AAMI validation process describes two analytic methods, which compare three automated paired readings from each of at least 85 participants versus reference BP values obtained by a manual auscultatory method. In method 1, which was retained from the protocol of 1992, each individual test and reference reading was used in the statistical analysis leading to a mean (± 5 mmHg) and a large standard deviation of differences (± 8 mmHg). Method 2 describes the use of averages of test and reference readings for each participant to help reduce apparent measurement error from intra-subject variability. The current AAMI standard recommends that a device should pass both methods of analysis [33].

The first BHS protocol was published in 1990, primarily addressing testing of ambulatory BP devices, with a subsequent revision in 1993 that made it applicable to devices for intermittent monitoring of BP [35]. This method also requires measurements in 85 participants and a grading system for devices based on the percentage of readings within 5, 10 and 15 mmHg of the reference measurement. Devices with grade less than 'B' are not considered acceptable for clinical use. The BHS protocol also calls for five phases of validation:

1. Before use device validation
2. In-use (field) assessment
3. After-use device calibration
4. Static device calibration where the device is rechecked after 1 month of usage
5. Report of evaluation.

Each phase has separate passing criteria [32, 35]. Though the AAMI and BHS protocol have different acceptance criteria, the requirements for device performance are fairly similar [33, 34].

The ESH published a new protocol — the International Protocol — in 2002, with the intent of providing a simplified method of validation [32]. This protocol has required measurements in far fewer participants and devices that did not meet the initial criteria in the first 15 participants were not tested further and were eliminated at an early stage, thus saving considerable time and cost. The International Protocol also tests devices for intra-subject variability and uses a passing or failing grading system. The International Protocol has not been widely accepted by regulatory bodies because of concern about low statistical power for demonstrating reliable differences for new devices versus a reference standard [33]. There has also been criticism that the International Protocol differs too much from previous protocols and does not require specifications about the range of arm circumference over which devices must be tested nor does it specify the maximum number of subjects that can be excluded [33].

It is noteworthy that not all automated BP devices in the marketplace have been properly validated. To assist the user of devices in making decisions regarding a particular automated BP recorder, a list of validated monitors has been made available on the dabl Educational Trust website (<http://www.dableducational.org>). It is also important to note that even devices that have been validated may not provide accurate readings in special types of patients, hence, it is recommended that automated devices should be assessed on special patient

populations (e.g. elderly, pregnant, children) before they are considered valid for broad clinical use [27].

Types of self-BP monitors available for clinical use

Monitors have been developed that record BP from the upper arm, wrist, or finger. Monitors that measure pressure at the wrist and fingers have become popular with patients due to ease of use, but there are concerns regarding the attenuation of systolic and diastolic pressures in the more distal sections of the arterial tree. In general, the systolic pressure increases in more distal arteries, whereas the diastolic pressure decreases. Moreover, the position of the wrist relative to the level of the heart leads to large variations in BP from hydrostatic effects. Patients must be educated to ensure that the wrist is held at heart level during BP measurements.

Measurements from finger devices are of even greater concern as they also are affected by the position of the hand, by peripheral vasoconstriction associated with ambient temperatures, and other environmental factors (e.g. smoking). Most of the finger BP devices have not been validated.

Patients often take their BP in locations other than home (pharmacies and other retail stores, schools, BP screenings performed in the community, and other worksite environments). Devices available in public areas such as pharmacies and retail stores are often not routinely calibrated; do not have variable arm cuff and bladder sizes and may yield inconsistent results; their use for routine self-BP monitoring is not recommended.

How many self-BP measurements should patients take?

As the reproducibility of home BP is dependent on the number of readings available, it is important to inform patients as to how many measurements are needed over a time period to ensure a reliable estimate of true BP. The ASH, the AHA and the ESH guidelines suggest taking at least two morning and two evening readings every day for a minimum of 1 week but to discard the readings of the first day, which gives a total of 24 readings on which to make clinical decisions both for initial diagnosis and interval follow-up of hypertensive patients [13, 27].

Of great importance are the definitions of normal versus hypertensive SBP measurements. Home BP values are usually lower than clinic BPs and the consensus paper of the ASH [36] suggests that a seated self-monitored BP of 135/85 mmHg corresponds to a clinic pressure of 140/90 mmHg. However, there are no official guidelines on self-BP values in high-risk populations with desired clinic BP $\leq 130/80$ [36]. Studies using regression analyses of office, home and ambulatory BP suggest that in order to have a normal ($<130/80$ mmHg) 24-h average BP, the home BP should average $<126/76$ mmHg [1, 36] (Table 4.2).

Transtelephonic self-monitoring of blood pressure

Transtelephonic monitoring is an advanced technology for self-BP measurement intended to decrease the reporting bias when home BP measured by patients is reported with intentional or unintentional errors in recording. Transtelephonic devices have a telephone cord receptacle that allows patients to insert their telephone jack from their analog phone system to the self-BP device. This allows data to be transferred via a central server to the physician or nurse office. Data are provided in a tabulated and analyzed form for clinical decision making and may be more efficient than an office visit based management system where the physician may spend considerable time in interpreting data self-recorded by patients. Though a few studies have demonstrated better BP control in telemedicine managed groups [37, 38]; the cost of system setup and maintenance is considerable and the technology has not been widely used.

Table 4.2 Features of different methods of BP measurement (with permission from the American Heart Association [5])

	Clinic	Home	Ambulatory
Predicts outcome	Yes	Yes	Yes
Initial diagnosis	Yes	Yes	Yes
Upper limit of normal	140/90	135/85	135/80 (24-h) 135/85 (day) 120/75 (asleep)
Evaluation of treatment	Yes	Yes	Limited
Assess diurnal rhythm	No	No	Yes
Cost	Inexpensive	Inexpensive	Moderate

In contrast, transtelephonic BP monitoring has been quite successful in clinical research trials in which frequent measurements are required to evaluate the safety or efficacy of a pharmacotherapy [39]. In a recent study of over 400 patients with Parkinson Disease [39], the monoamine oxidase inhibitor rasagiline was studied over a 9-month period using transtelephonic BP recordings before and after meals. The technology was ideal for evaluating postprandial changes in systolic BP.

AMBULATORY BLOOD PRESSURE MONITORING (ABPM)

In contrast to self- or home BP monitoring, ABPM provides automated BP measurements over a period of 24 h or longer while patients are engaged in their usual daily activities and during sleep. Previously used only in hypertension and cardiovascular research, ABPM has become a more clinically oriented procedure in which numerous benefits are derived including avoidance of observer error, terminal digit bias and the white-coat effect.

Ambulatory BP monitoring also provides a large enough number of readings throughout the day and night to more comprehensively evaluate BP behavior compared to office or home BP measurements. Blood pressure has a circadian variability that is characterized by higher BP levels during mental and physical activity, lower BP values during sleep and rest, and an early morning surge lasting 3 to 5 h during the transition from sleep to wakefulness [1, 34]. Most patients have a 10% or greater decline in nocturnal BP compared with their awake BP and are referred to as 'dippers'. This response may be blunted or absent in 10–30% of patients who are 'non-dippers' or reversed in a small proportion of patients exhibiting 'reverse dipping' in which nocturnal BP may be higher than day time readings. This may be because of autonomic dysfunction or certain causes of secondary hypertension [34, 40]. Multiple studies have shown that hypertensive end-organ damage is more likely in non-dippers than in dippers [40, 41] and thus it may be clinically relevant to identify patients as such.

Modern ABPM devices are lightweight compact units that have become a bit larger than a cell phone and can be worn without much inconvenience [34]. The devices are validated according to the criteria discussed previously [31, 32, 35] and measure BP by the oscillometric technique. The ABP recorder can be programmed for rate and degree of inflation and deflation and to take BP at specified intervals, usually every 15 min during the awake period and every 30 min during the sleep period. Some devices have a feature for patient-initiated readings, which can be used to monitor BP at the time of symptom(s). It is preferable to do the study on a regular working day and patients should be educated to maintain their usual schedule for estimation of true BP, but should avoid heavy physical activity during read-

Table 4.3 Suggested values for the upper limit of normal ambulatory BP (mmHg) (with permission from the American Heart Association [5])

	Optimal	Normal	Abnormal
Daytime	<130/80	<135/85	>140/90
Night-time	<115/65	<120/70	>125/75
24-h	<125/75	<130/80	>135/85

ings, which can interfere with the measurements. It is important to instruct the patient to hold the arm still by the side while the device is taking a reading. Usually the patient is asked to keep a diary recording the time of medication, symptoms, activity level, and sleep and awake time.

Upon completion of the 24-h BP study, the data is downloaded to a dedicated software program (depending on the device manufacturer) and statistically analyzed to calculate average BPs over 24 h, during awake time and sleep time as well as during the period while the patient is in the medical care environment (the 'white-coat' period). At least 75 to 80 valid measurements should be obtained for a 24-h study [34]. The averages are reported along with the standard deviations of the mean to provide an idea of BP variability. Some studies have indicated that patients who have greater than average BP variability have significantly more hypertensive end-organ damage [42–44]. Another clinically useful calculation is that of the BP load, which is the proportion of BPs above normal, calculated separately for awake and sleep periods; however, this parameter is not useful in patients with severe hypertension. Higher BP loads are independently predictive of hypertensive cardiac involvement, left ventricular hypertrophy (LVH), increased peripheral resistance and hypertensive retinopathy [44–46] (Table 4.3).

Prospective studies in hypertensive patients have demonstrated that ABPM is a more accurate predictor of cardiovascular risk and progression of end-organ damage than conventional BP measurements [34, 36, 47]. The primary indications for ABPM are the evaluation of suspected white-coat and resistant hypertension. It can also be used as an important clinical tool in the assessment of episodic hypertension or hypotension and autonomic dysfunction. Ambulatory BP monitoring is however limited in patients with atrial fibrillation or frequent ectopic beats and those with mid arm circumference of >40 cm [34]. There is evidence that ambulatory BP measurements have superior reproducibility compared with office BP when repeated over a period of several months to 2 years, making it unnecessary to repeat on a frequent basis in relatively stable patients [48].

SUMMARY

Given the advantages and limitations of different methods of blood pressure monitoring each method has its utility in clinical practice. Office BP measurement is an invaluable tool in the management of hypertension, providing physician input not just in the interpretation of BP values but also educating patients about blood pressure goals and assessing for drug effects and interactions and other comorbid conditions. Use of self-monitoring can help identify and overcome issues of white-coat effect and observer bias. Patient involvement in their own care also empowers patients and helps increase awareness for prevention of hypertension related end-organ damage. However, patients need to be educated in the proper technique of BP measurement and in the recording of data so it can be interpreted in a meaningful way. They should also be assisted in the selection of reliable and validated devices and wrist and finger devices should be avoided if possible. In cases of resistant

hypertension or conflicting values between office and home blood pressures, further assessment with 24-h monitoring can give a better idea of the true BPs and also provide information on diurnal variation and BP loads, which have also correlated with progression of end-organ damage.

A better understanding of hypertensive monitoring and treatment can enhance our ability to improve hypertension care on a global level and deal with this important public health challenge.

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Is blood pressure control more important than decreasing activity in the renin-angiotensin axis?

W. J. Elliott

BACKGROUND

One of the most controversial topics in hypertension today is whether specific antihypertensive drugs (or drug classes) convey “*benefit beyond blood pressure (BP) lowering*.” Much of the impetus for this concept is derived from marketing efforts of pharmaceutical companies to distinguish their particular drug or drugs from others in the crowded antihypertensive drug marketplace. Although the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [1] does not mention the issue, more recent European guidelines have concluded, “*the main benefits of antihypertensive therapy are due to lowering of BP per se*” [2]. Like other aspects of nearly all clinical guidelines, this pronouncement has not met with universal agreement, and very detailed ‘debates’ about the concept have been published [3, 4] and presented in national and international meetings. The purpose of this chapter is to review the controversy and attempt to answer a few important questions about this general topic that are even more contentious.

DATA FROM INDIVIDUAL TRIALS CONSISTENT WITH ‘A BENEFIT BEYOND BP LOWERING’

Historically, the claim that certain antihypertensive drugs offered a “*benefit beyond BP reduction*” started with the Heart Outcomes Prevention Evaluation (HOPE) [5]. In this clinical trial that changed prescribing habits [6], the 4645 subjects who received ramipril (BP ~136/76 mmHg) enjoyed a highly significant 22% reduction in the incidence of the composite end-point of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke, compared with the 4652 subjects randomized to placebo (BP ~139/77 mmHg). The HOPE investigators reported that this benefit was far out of proportion to the tiny 3.3/2 mmHg difference in average blood pressure between the groups, and therefore should be attributed to the drug itself. Several unusual or unique aspects of the HOPE trial deserve mention. HOPE was the first trial to dose ramipril at bedtime (presumably to minimize daytime hypotension), but the clinic BPs were not taken at any specific time of day. In fact, the protocol required only five BP measurements throughout the 4.5-years of follow-up, so the ability to detect serial BP differences across the randomized groups may not have been very great. Secondly, 38 HOPE

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subjects with peripheral arterial disease having office BPs about 150/81 mmHg at baseline underwent 24-h ambulatory BP monitoring [7], and the difference in BPs across the randomized groups was significant at year 1 (24-h BP difference: 10/4 mmHg, nocturnal BP difference: 17/8 mmHg); both differences were much larger than the BP difference seen in the entire HOPE cohort. Thirdly, HOPE allowed physicians to add or adjust doses of antihypertensive drugs during follow-up, so the group randomized to placebo may have received more non-ACE inhibitor drugs than the group randomized to ramipril after randomization. Lastly, in meta-regression analyses (discussed below), HOPE is unique among trials, as its result lies outside the 95% confidence intervals derived from 27 clinical trials involving 136 124 patients [8].

The second trial in which a blocker of the renin-angiotensin-aldosterone system (RAAS) might have been associated with a benefit *"beyond BP lowering"* was seen with the composite renal endpoint of the Irbesartan Diabetic Nephropathy Trial [9]. Because this trial included a *"positive-control"* (i.e. amlodipine), the authors were better able to dissect the BP-dependent and independent effects of the randomized treatments. The mean BPs during follow-up were: 140/77 mmHg for irbesartan, 141/77 mmHg for amlodipine, and 144/80 mmHg for placebo, and the relative risk reductions for the composite endpoint of doubling serum creatinine, end-stage renal disease, or death for irbesartan were 20% (compared with placebo) and 23% (compared with amlodipine). These data suggest overall that the beneficial effect of irbesartan on the renal endpoint (especially compared with amlodipine) was unlikely to be due to BP control. However, the incidence of secondary composite cardiovascular events across the treatments was not significant, paralleling the responses of the drugs' BP-lowering effects.

Much attention was directed to the results of the Losartan Intervention For Endpoint (LIFE) reduction in hypertension trial, which were also interpreted as showing that losartan had *"benefits beyond BP lowering."* After washout of all antihypertensive drugs, 9193 hypertensive subjects with strict echocardiographic evidence of left ventricular hypertrophy (LVH), were randomized to either losartan or atenolol, followed in each case by the identical doses of hydrochlorothiazide. Seated BPs were nearly identical at randomization (174.3/97.9 vs 174.5/97.7 mmHg, respectively), and fell by an average of 30.2/16.6 and 29.1/16.8 mmHg, respectively at the final visit (or the visit prior to an event). Although this BP difference favored the losartan-treated group (by only 1.4/1.0 mmHg), the results of the composite primary endpoint (myocardial infarction, stroke or cardiovascular death) showed a significant 13.0% reduction with losartan, even after adjustment for baseline Framingham risk score and degree of LVH. The authors interpreted their data by saying, *"the greater cardiovascular protective effect of losartan compared with atenolol is due to benefits beyond BP reduction and LVH regression."*

Perhaps the strongest case can be made from data gathered in the MORbidity and mortality after Stroke, Eprosartan compared with nitrendipine for Secondary prevention (MOSES) trial [10]. In this German multicenter study, 1405 hypertensive subjects with a proven stroke in the prior 24 months were randomized to start antihypertensive therapy with either nitrendipine (a calcium antagonist with proven benefits in primary stroke prevention) or eprosartan. The primary endpoint was the total cardiovascular burden of mortality and cardiovascular and cerebrovascular events (including recurrent events). After a mean of 2.5-years of follow-up, BP was slightly lower in the eprosartan group (by about 1.5/0.6 mmHg), but there were significantly fewer outcomes in the eprosartan-treated group. Unfortunately, when only the data about first events were analyzed, only the cardiovascular endpoints retained statistical significance, perhaps because of the small numbers of subjects with events. Nonetheless, MOSES is the only comparative drug trial in which the randomized arm achieving the lower BP was significantly inferior to the comparator in preventing cardiovascular events.

The majority of, if not all of, the world's literature comparing drug therapies for hypertension suggests that the major impact on cardiovascular prevention is directly related to BP

lowering, although *caveats* exist. There is still concern about “lowering BP too far” in patients with coronary heart disease (CHD) [11], and purists will argue that the Hypertension Optimal Treatment’s (HOT’s) primary analysis showed no significant differences in cardiovascular events among hypertensive subjects randomized on treatment and with diastolic BPs of ≤ 80 , ≤ 85 , or ≤ 90 mmHg [12].

IMPORTANT QUESTIONS

IF BP IS BROUGHT TO A LOW-ENOUGH LEVEL, DOES IT MATTER WHETHER AN ACE-I IS BEING USED IN THE HIGH-RISK PATIENT?

The answer to this important question depends to a certain extent on the definitions of “high-risk patient” and “BP at a low-enough level.” Although brachial BPs have been long used because of convenience and simplicity, abundant recent data indicate that ambulatory BP monitoring provides a more complete picture of the extent and timing of BP elevations, and add predictive value about outcomes, even over and above office BP measurements. For this reason, many hypertension clinical trials now include ambulatory BP monitoring substudies. Most such substudies do not find significant differences between office BP measurements and 24-h ambulatory BP monitoring; however, HOPE appears to be an exception in finding a large difference in BPs in the substudy, compared to the main trial [7]. Another consideration has been raised since the Conduit Artery Function Evaluation substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), in which large differences were seen between BPs measured in the brachial artery, and those estimated in the central aorta [13]. While this difference has been attributed specifically to the β -blocker atenolol used in ASCOT, it raises the possibility that BPs achieved in different vascular beds may have differential effects on prognosis.

Since HOPE, a “high-risk patient” has been defined (even by the United States Food and Drug Administration (FDA), in their unique indication for ramipril “in patients over the age of 55 years at high cardiovascular risk, to reduce the risk of myocardial infarction, stroke, or death from cardiovascular disease”) as a “person with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes mellitus that is accompanied by at least one other cardiovascular risk factor (hypertension, elevated total cholesterol level, low high-density lipoprotein (HDL)-cholesterol level, cigarette smoking, or documented microalbuminuria).” Since HOPE, there have been three other trials that randomized patients with these (or more stringent) criteria (but without heart failure) to treatment with an ACE inhibitor or placebo, in addition to whatever other cardiovascular medications were needed, according to the treating physician.

The Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) trial enrolled 6105 survivors of a cerebrovascular event (84% with a stroke in the last 5 years, 16% with a transient ischemic attack), and randomized them to either placebo or perindopril [14]. The randomization was stratified because many physicians felt that the use of two drugs initially might lower the BP “too far,” so only 58% of the randomized patients received the combination of perindopril + indapamide (as originally recommended), and 42% received only the ACE inhibitor. Although the primary outcome was recurrent stroke, the investigators reported a significant 40% reduction in major cardiovascular events (myocardial infarction, stroke, or cardiovascular death) in the group randomized to initial ACE inhibitor therapy (whether or not they received concomitant diuretic therapy with it, resulting in a BP difference of 9/4 mmHg). Among the 50% of subjects with hypertension at randomization, there was a 29% reduction in this composite endpoint (and an average BP difference of 9.5/3.9 mmHg). Importantly, however, when the data were broken down by the stratified randomization (initial *vs* combination therapy), those who received only the ACE inhibitor had but a 5/3 mmHg reduction in BP, and only a non-significant 4% reduction in cardiovascular events, whereas those who received BOTH the ACE inhibitor AND the diuretic enjoyed a

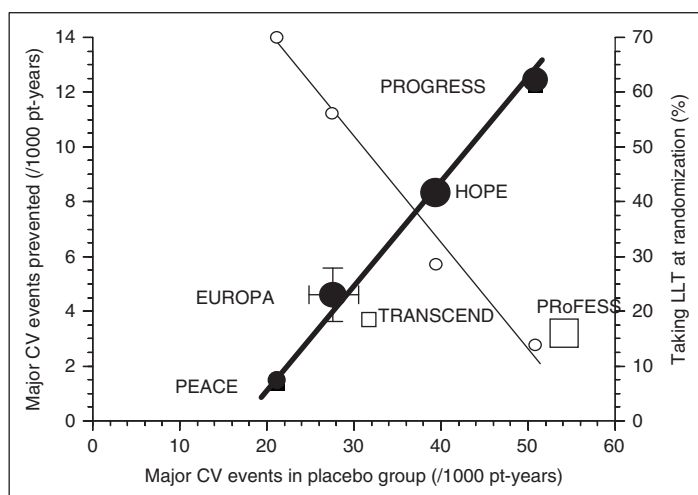


Figure 5.1 Correlations between the absolute risk of cardiovascular (CV) events (using the primary outcome of the Heart Outcomes Prevention Evaluation [HOPE]: non-fatal stroke, non-fatal myocardial infarction, or cardiovascular death) in the placebo group (expressed per 1000 patient [pt]-years of observation) and: (a) (dark line connecting filled circles, drawn with area proportional to the number of subjects with events in each trial) the number of cardiovascular events prevented in the large placebo-controlled trials of angiotensin converting-enzyme inhibitors (in circles) and angiotensin II receptor blockers (as squares, which don't fit the line), (b) (light line connecting open circles of constant area) the proportion of the study population in each trial that were taking lipid-lowering therapy (LLT) at randomization. The correlation coefficients (and P -values) for these relationships were: (a) $r = 0.996$, $P < 0.001$; (b) $r = 0.991$, $P = 0.008$. The 'error bars' on the circle labeled, 'EUROPA' are the 95% confidence limits, as the numbers of patients in EUROPA with the HOPE primary endpoint are not published (adapted and updated with permission from [17]). EUROPA = EUROpean Reduction Of cardiac events with Perindopril in stable coronary Artery disease; PEACE = Prevention of Events with Angiotensin Converting-Enzyme inhibition; PRoFESS = Prevention Regimen For Effectively avoiding Second Strokes; PROGRESS = Perindopril pROtection aGainst Recurrent Stroke Study; TRANSCEND = Telmisartan Randomised Assessment Study in ACE iNtolerant subjects with cardiovascular Disease.

12/5 mmHg reduction in BP and a highly significant 40% reduction in cardiovascular events. These are the only data from a placebo-controlled trial that can compare monotherapy and combination therapy involving a RAAS blocker; they suggest that little benefit accrues to those who receive only an ACE inhibitor, but major benefit occurs when BP is further reduced with two drugs.

The third study that compared an ACE inhibitor with placebo in "high-risk" patients was the EUROpean Reduction Of cardiac events with Perindopril in stable coronary Artery disease study (EUROPA) [15]. Like PROGRESS, the EUROPA study population of 12 218 subjects was more homogeneous than in HOPE, as all patients had documented coronary heart disease. Because of this, the EUROPA primary endpoint was cardiac arrest, myocardial infarction, or cardiovascular death (with stroke recorded separately). As in HOPE, the randomization was to perindopril or placebo, again in addition to whatever other medications were deemed appropriate by the treating physician. After a mean of 4.2-years of follow-up, BP was 5/2 mmHg lower in the perindopril group, which also enjoyed a highly significant 20% reduction in the primary endpoint.

The US National Institutes of Health funded the fourth trial, the Prevention of Events with Angiotensin Converting-Enzyme inhibition (PEACE) study, which compared trandolapril against placebo in 8290 subjects with stable coronary disease and known normal or only

slightly reduced left ventricular function [16]. Less than half the subjects had hypertension at randomization, and the BP differences at 3-years of follow-up were only 3/1.2 mmHg (129/74 for trandolapril *vs* 131/75 mmHg for placebo), which was significant. Perhaps because the study was largely done in the USA and the subjects were intensively treated with other cardioprotective drugs, the primary endpoint of myocardial infarction, coronary revascularization, or cardiovascular death was reduced by a non-significant 4%. If the HOPE primary endpoint had been used in the PEACE study, trandolapril would have lessened its occurrence by only 7%.

Many authors have attempted to find a suitable unifying explanation for these rather disparate results of giving an ACE inhibitor or placebo, in addition to other required drugs, to “*high-risk*” patients. Although the in-treatment BP is highest for the ramipril-treated HOPE subjects (132/74 mmHg), there is no relationship between the benefits observed and the in-treatment BPs for those receiving ACE inhibitors across these trials. The simplest explanation has been offered previously [17], based on the reduction in absolute risk of the HOPE primary endpoint in each trial (Figure 5.1), presumably due to the more intensive treatment (with aspirin, β -blockers, and especially HMG-CoA reductase inhibitors) in the later trials, compared to HOPE. In fact, the correlation of the percentage of subjects taking HMG-CoA reductase inhibitors at baseline with the reduction in cardiovascular events across the four trials is highly significant ($r = 0.99$; $P < 0.008$). This observation is consistent with the conclusion of others: true “*benefits beyond BP lowering*” are most easily realized when antihypertensive therapy is combined with multiple risk factor reduction [18, 19]. Unfortunately, recent data from the Telmisartan Randomised Assessment Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND [20]) and Prevention Regimen For Effectively avoiding Second Strokes (PROFESS [21]) trials do not fit the relationship (squares in Figure 5.1). But the simple answer to the question about ACE inhibitors is: if the absolute risk of a high-risk patient is maximally reduced, it is unlikely that any further protective intervention (including an ACE inhibitor) will prove significant.

WHAT BENEFITS DOES AN ACE-I OFFER “BEYOND BP REDUCTION”?

There are several different methods of attempting to address this question. The simplest and most intellectually appealing is to design and execute a well-performed randomized clinical trial that compares an ACE inhibitor with a different active antihypertensive drug, control the BPs to exactly the same degree, and compare the outcomes across the two randomized arms. Unfortunately, this study has yet to be done.

A different approach has been taken *post hoc* in clinical trials in which BP reductions were unequal across arms after randomization [22–24]. “*Serial median matching*” is a technique that uses a subset of the trial’s subjects, matching individuals from each randomized arm with the same BPs, and then comparing outcomes in a matched case–control fashion. Despite its inherent flaws, this technique has not yet been applied to a hypertension clinical trial involving a first-line ACE inhibitor.

A third statistical method for attempting to identify BP-independent effects of an antihypertensive treatment is to perform a meta-regression of the odds ratio for cardiovascular events against the mean difference in (systolic) BPs between the two randomized groups (Figure 5.2). Two methods of interpreting these plots have been used: the first compares the number of ‘outliers’ (those trials having results beyond the 95% confidence limits for a large number of prior studies) with the number expected; the second assesses whether the 95% confidence limits at no difference in BP includes or excludes “*no benefit*” (i.e. odds ratio = 1.00). The former approach can include all trials that used a specific initial drug class, regardless of comparator (e.g. ACE inhibitor *vs* any other) [4, 8]; the latter is more limited, as it involves only trials comparing two specific classes of drugs (e.g., ACE inhibitor *vs* calcium

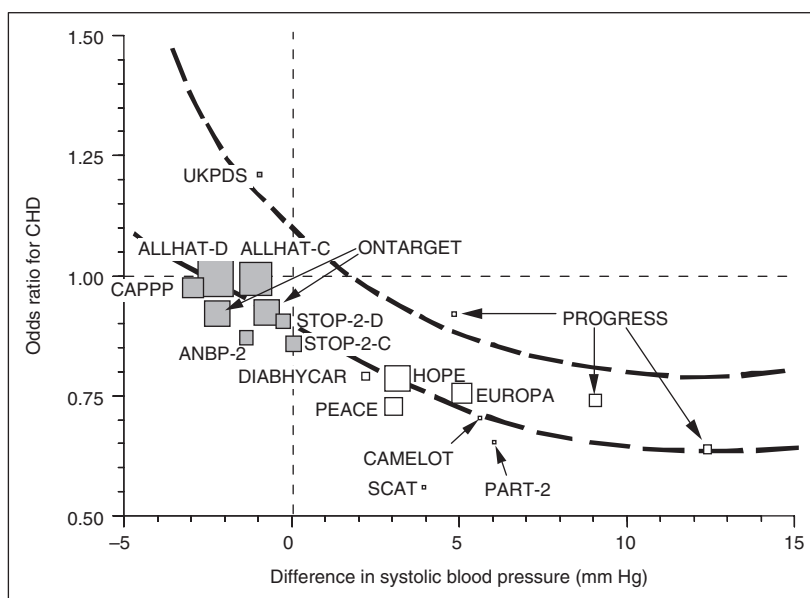


Figure 5.2 Meta-regression plot of the systolic blood pressure difference between randomized arms and the odds ratio for coronary heart disease (CHD) events in clinical trials involving angiotensin converting-enzyme (ACE)-inhibitors in hypertensive patients. The 'dotted lines' correspond to the 95% confidence limits for the analogous plot involving all 27 drug trials in 136 124 hypertensive patients completed prior to 2001 [8]. The 95% confidence limits for the regression line drawn through the squares do not include the origin, leading some authors to claim "benefit beyond BP lowering" for ACE inhibitors on CHD. The placebo-controlled studies are shown as open squares; the actively-controlled trials are shaded. Each trial is represented by a square in proportion to the number of CHD events observed in the designated arms of the study. There were so few CHD events in several trials that their squares cannot be seen at the resolution of the figure. ALLHAT-C = the calcium channel blocker (CCB) arm of the same trial; ALLHAT-D = diuretic arm of the Antihypertensive and Lipid Lowering to prevent Heart Attack Trial (ALLHAT); ANBP-2 = Second Australian National Blood Pressure Trial; CAMELOT = Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis; CAPPP = Captopril Primary Prevention Project; ONTARGET = Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoints Trial (two comparisons: combination vs. ramipril on the left, telmisartan vs. ramipril on the right); SCAT = Simvastatin/enalapril Coronary Atherosclerosis Trial; STOP-2-C = CCB arm of the Swedish Trial in Old Patients with Hypertension #2; STOP-2-D = diuretic/beta-blocker therapy arm of the Swedish Trial in Old Patients with Hypertension #2; UKPDS = United Kingdom Prospective Diabetes Study (other trial acronyms are expanded in the text).

antagonist) [25, 26]. Many trials are necessary for the former, because it results in a qualitative judgment of how many trials fall outside the expected limits, whereas the latter method can provide an estimate of the magnitude (and statistical significance) of the BP-independent portion of the observed effect. Thus, when all available trials involving ACE inhibitors are included, and the odds ratio for CHD events plotted *vs* the average observed BP differences for each randomized comparison (Figure 5.2), nearly all of the 'dots' fall within the 95% confidence limits of the regression line derived from all clinical trials completed prior to 2001. Verdecchia *et al.* were the first to compare ACE inhibitors with calcium antagonists in preventing CHD or stroke [25]. Their analysis included only trials that involved one or both of these drug classes, and concluded that BP lowering was a very significant predictor of both CHD and stroke prevention, but that there was a barely significant residual effect, independent of BP for ACE inhibitors on CHD events ($P = 0.028$), and for calcium antago-

nists on stroke ($P = 0.042$). Neither of these, of course, would be considered statistically significant if corrections were made for multiple comparisons. The alleged “BP-independent effect” of ACE inhibitors on CHD is also heavily influenced by the results of HOPE and EUROPA; if these trials are omitted (because either the majority of their subjects were not hypertensive, or ACE inhibitors were not initial therapy in either trial), there is no significant residual “BP-independent” effect of ACE inhibitors on CHD.

More recently, the Blood Pressure Lowering Treatment Trialists’ Collaboration has performed similar analyses (but comparing ACE inhibitors and ARBs), using the patient-level database acquired from the principal investigators of all large trials since 1998 [26]. They also concluded that “the size of BP reduction achieved with either drug class is directly associated with the size of the reductions in stroke, CHD, and heart failure.” As with Verdecchia, they detected a significant 9% reduction (95% confidence interval 3 to 14%) in the relative risk of CHD associated with ACE inhibitor use that was “independent” of the BP differences seen in the trials. They suggested that this effect was about equal to that of a further drop of 3 mmHg in systolic BP, and remained when the HOPE data were excluded from the analysis. Proponents of the theory that ACE inhibitors have important BP-independent protective effects against CHD have pointed to the Antihypertensive and Lipid-Lowering to prevent Heart Attack Trial (ALLHAT) data as “proof” of this concept. In ALLHAT, the 9060 subjects originally randomized to lisinopril conceded at least 2 mmHg of systolic BP throughout the entire 4.9 years of follow-up (and more than 6 mmHg in the Black subjects during the first 6-months), and yet experienced 1% less CHD than the 15 268 subjects initially randomized to chlorthalidone [27].

In sum, therefore, one can make an evidence-based argument that ACE inhibitors may have a BP-independent effect in preventing CHD, but one must admit that not all data and not all analyses support this hypothesis.

DO THE BP-INDEPENDENT EFFECTS OF AN ACE-I DEPEND ON THE DOSE BEING USED?

This is a much more challenging question, as the existence of BP-independent effects of ACE inhibitors is controversial, and there is little direct evidence pertaining to cardiovascular disease. Very few studies have randomized subjects to low- or high-dose ACE inhibitors and compared outcomes across the randomized groups. One study in patients with heart failure showed that a higher dose of lisinopril was associated with a non-significant trend for reducing mortality (the primary endpoint), but a significant benefit on a secondary composite endpoint of mortality or hospitalization [28].

For renal disease outcomes, the importance of dose has been well-addressed recently [29], and the arguments presented may also be pertinent to cardiovascular disease. Data suggest that both ACE inhibitors (and ARBs) have BP-independent benefits in reduction of albuminuria/proteinuria [30], and perhaps even in preventing doubling of serum creatinine, end-stage renal disease and death [9], although even this is controversial [31].

Two pairs of placebo-controlled studies with high and low doses of ACE inhibitors that compared cardiovascular disease outcomes suggest that the dose is quite important, with higher doses being associated with better outcomes. Few remember the DIABetes, HYpertension, microalbuminuria or proteinuria, Cardiovascular events And Ramipril (DIABHYCAR) trial [32] as well as the MICOalbuminuria, Cardiovascular and Renal Outcomes substudy of the Heart Outcomes Prevention Evaluation (MICRO-HOPE) substudy of the HOPE trial [33]. In the former, 4912 diabetics with microalbuminuria were randomized to placebo or 1.25 mg/d of ramipril, and followed for 4 years. BP was reduced in the low-dose ramipril group by 2.4/1.1 mmHg, but there were no significant improvements in either albuminuria regression ($P = 0.07$) or cardiovascular events ($P = 0.64$). In contrast, in the latter, 3577 diabetics were randomized to placebo or 10 mg/d of ramipril, and followed for 4.5 years. The 1808 subjects who received the high-dose ramipril had about

4 mmHg lower systolic BP after 1 month of treatment, but this decreased to about 2.4 mmHg by the final visit. More importantly, the high-dose ramipril group enjoyed a highly-significant 25% reduction in the HOPE primary endpoint, as well as a significant reduction in each of its components, as well as a significant decrease in the incidence of proteinuria (≥ 300 mg/d) [33]. Although there were a few differences in the baseline characteristics of the subjects in DIABHYCAR and MICRO-HOPE (e.g. average age: 65 *vs* 65 years, duration of diabetes 10 *vs* 11 years, 70% *vs* 65% male, 56% *vs* 56% hypertensive), it is tempting to speculate that the major difference in outcomes was due to the different doses of ramipril.

A second trial done comparing placebo to ramipril (either 5 or 10 mg/d, whichever could be tolerated in the short-term) involved 617 subjects with coronary or other occlusive vascular disease, followed for 4 years to assess carotid atherosclerosis and LVH [34]. Although the BP was reduced, on average, by 6/4 mmHg in the ramipril group, there were no difference in ultrasound measurements between the randomized groups. Although not powered to detect differences in cardiovascular events, there were no significant differences across the groups in any outcome: stroke was more common in the ramipril group (7 *vs* 4), non-fatal myocardial infarction was nearly equal (18 *vs* 19), but cardiovascular death favored ramipril (8 *vs* 18), as did fatal or non-fatal CHD (22 *vs* 33). Although there were many differences between this study and HOPE (especially regarding sample size), one wonders if the lower dose of ramipril may have caused the results to be so different from those seen in HOPE.

Relatively little attention has been focused on whether the reduction in albuminuria/proteinuria seen in placebo-controlled trials with ACE inhibitors is dose-dependent, despite many analyses and meta-analyses [35–37]. Because the effects of ACE inhibitors and ARBs on BP-lowering and albuminuria/proteinuria are similar [30, 38], one might suspect that studies addressing this issue with ARBs might be relevant. The first large trial to specifically study “usual doses” of an ARB on the development of albuminuria was the second IRbesartan MicroAlbuminuria (IRMA-2) trial. In this multinational study, 590 patients with hypertension, microalbuminuria, and type 2 diabetes were randomized to placebo or one of two doses (150 or 300 mg/d) of irbesartan and followed for 2 years for development of persistent albuminuria in overnight specimens [39]. The 300 mg/d dose of irbesartan was statistically superior to placebo in forestalling the onset of clinically determinable proteinuria, but the 150 mg/d dose was not, although its effects were numerically intermediate [39]. Recently, “supra-therapeutic” doses of ARBs have been found to reduce albuminuria/proteinuria even more than the highest dose used to lower BP [40–42], as have studies that combined two inhibitors of the RAAS [30, 42, 43]. Thus, the question of dose and a BP-independent effect has been better answered with renal endpoints and ARBs than it has with ACE inhibitors and cardiovascular endpoints [44, 45].

IS THERE A DIFFERENCE BETWEEN ACE-I AND ARBS IN THE HIGH-RISK CORONARY ARTERY DISEASE (CAD) PATIENT?

The simplest and most direct answer to this question is likely to have come from the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), which compared cardiovascular outcomes in high-risk CVD patients randomized to ramipril, telmisartan, or the combination [46]. The simple conclusion obtained from ONTARGET was that the ARB and the ACE inhibitor were “*equivalent*” (as regards cardiovascular outcomes), but that the combination had more side-effects (especially adverse renal outcomes) [47]. Approximately 74% of the ONTARGET patients had coronary disease, and although the results of comparisons in this specific subgroup have not yet been made public, the results in all other subgroups have apparently been consistent with the main conclusion of the study. These data would suggest that the answer to the question is likely to be, “*not for cardiovascular event prevention, but there is a difference regarding side-effects and cost.*”

Table 5.1 Results of network meta-analyses of clinical trials involving ‘high-risk’ patients treated with ACE inhibitor, angiotensin II receptor blocker (ARB), or placebo (referent agent)

<i>Event</i>	<i>Odds ratio (95% CI) vs placebo</i>		<i>P-value*</i>	<i>Incoherence</i>
	<i>ACE inhibitor</i>	<i>ARB</i>		
Death	0.95 (0.84–1.08)	0.98 (0.86–1.12)	0.687	0.0627
CV death	0.87 (0.78–0.97)	0.89 (0.78–1.01)	0.745	0.000002
Coronary heart disease	0.79 (0.72–0.86)	0.87 (0.76–1.00)	0.167	0.000004
Stroke	0.83 (0.69–1.01)	0.84 (0.69–1.03)	0.906	0.0787
Major CV event	0.84 (0.77–0.92)	0.87 (0.77–0.97)	0.653	0.000004
Heart failure	0.77 (0.70–0.86)	0.96 (0.83–1.10)	0.0066	0.000000000000004

* For the comparison of ACE inhibitor vs ARB. Trials: PROGRESS, HOPE, EUROPA, SCAT, PART-2, DIAB-HYCAR, PEACE, ONTARGET (monotherapy only), ACCESS, TRANSCEND, and PRoFESS (acronyms expanded in text). CI = confidence interval; CV = cardiovascular.

Since the publication of the ONTARGET results, two more studies (Telmisartan Randomised Assessment Study in ACE intolerant subjects with cardiovascular Disease, TRANSCEND [48], and Prevention Regimen for Effectively Avoiding Second Strokes, PRoFESS [49]) with ARBs in high-risk or post-stroke patients have been completed, neither of which showed telmisartan to be significantly superior to placebo for each trial’s primary endpoint. This superficial view has led some to conclude, particularly since HOPE and EUROPA were so positive for ACE inhibitors, ONTARGET was neutral, and TRANSCEND and PRoFESS were negative for ARBs, that ACE inhibitors should be considered superior to ARBs in the high-risk cardiovascular patient. However, the prespecified meta-analysis of TRANSCEND and PRoFESS published with the results of the former show that after combining the results of the two studies, there was significant prevention of both the ONTARGET primary endpoint (which included heart failure) and the HOPE primary endpoint (non-fatal stroke, non-fatal myocardial infarction, or cardiovascular death).

A somewhat more sophisticated answer to a related question (involving patients at high risk for cardiovascular disease, using the FDA’s definition, as above) can be provided by sub-jecting the results of many of the large trials discussed above (PROGRESS, HOPE, EUROPA, PART-2, PEACE, ONTARGET, ACCESS, TRANSCEND, and PRoFESS) to network meta-analysis, which includes the direct comparison of ramipril and telmisartan in ONTARGET, but adds the indirect comparisons of ACE inhibitors *vs* placebo and ARBs *vs* placebo. The results of these analyses (Table 5.1) show no significant differences between the ACE inhibitor and the ARB classes (except for heart failure), and both classes are numerically superior to placebo. These analyses are exceedingly superficial, of course, and ignore differences in absolute risk (e.g. Figure 5.1), on-treatment BPs (discussed above) and study populations.

SUMMARY

Although there is major controversy regarding the existence and potential clinical importance of “*benefits beyond BP lowering*” for the newer classes of antihypertensive drugs, there is abundant evidence from clinical trials, as relates to agents that block the RAAS, that their most important effect in preventing cardiovascular events is that they reduce BP. This may be best illustrated by the recent results of the Avoiding Cardiovascular events through COMbination therapy in Patients Living with Isolated Systolic Hypertension (ACCOMPLISH)

trial, in which both groups received comparable (and fairly high) doses of the ACE inhibitor, benazepril [50]. The group randomized to amlodipine ended up with a lower BP (by 0.9/1.1 mmHg), and significantly fewer cardiovascular events. Thus, using an antagonist of the RAAS in hypertensive patients at high risk for cardiovascular events is the easy part of the challenge; the more difficult issue is to reach the BP target, as an intermediate goal, that will ultimately reduce the incidence of cardiovascular and renal death and disability.

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6

Is there a class effect for all angiotensin-converting enzyme inhibitors when evaluating end-organ protection?

P. P. Toth, D. Sica

BACKGROUND

Angiotensin-converting enzyme (ACE) inhibitors (ACE-I) are highly effective agents for reducing blood pressure (BP) in patients with hypertension and they have an established role in the treatment of patients with cardiovascular (CV) disease [1]. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) identifies ACE-I as an initial drug choice for the treatment of hypertension (in combination with a thiazide type diuretic) [2]. Additional national guidelines recommend the use of ACE-I for CV disease management, including: the American College of Cardiology/American Heart Association guidelines for the management of heart failure (HF) [3]; the American College of Cardiology/American Heart Association Post-Myocardial Infarction Guidelines for management after myocardial infarction (MI) [4]; the National Kidney Foundation-American Diabetes Association for the management of hypertension and nephropathy in patients with diabetes mellitus [5]; and the National Kidney Foundation for the management of chronic kidney disease with or without hypertension [6]. Despite their proven efficacy, an issue of controversy in the use of ACE-I is whether there is a class effect for all ACE-I when evaluating end-organ protection. This chapter reviews the use of ACE-I and explores the clinical trials which supported their various clinical indications as well as the limitations of generalizing drug benefits to all ACE-I.

MECHANISMS OF ACTION OF ACE-I

ACE-I have a variety of mechanisms of action including promoting vasodilation, improving endothelial function by reducing oxidative stress, improving fibrinolytic balance, reducing adverse forms of remodeling in both myocardium and vessel walls, and inhibiting platelet activation, among others (Table 6.1) [7, 8].

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Table 6.1 Properties of angiotensin converting enzyme inhibitors (ACE-I) (adapted with permission from [7, 8])

- Promote vasodilation
- Limit neurohormonal activation and vasoconstriction during ischemia
- Improve endothelial function by reducing oxidative stress
- Slow down the development of atherosclerosis
- Improve fibrinolytic balance
- Inhibit platelet activation
- Reverse negative vascular remodeling

ACE-I improve the vasoconstrictive/vasodilatory balance by blocking the formation of angiotensin II and preventing the degradation of bradykinin [7, 8]. ACE-I inhibit the formation and binding of angiotensin II to angiotensin receptors and also modify the expression of receptors for angiotensin II and of other vasoactive hormones including bradykinin and adrenomedullin (Figure 6.1) [7]. Angiotensin II interacts with at least two receptor subtypes, AT_1 which results in vasoconstriction, release of aldosterone by the adrenal glands, and retention of salt and water; and AT_2 , which is upregulated in response to tissue injury and appears to exert effects on CV/renal tissue including vasodilation, a decreased chronotropic effect, and promoting natriuresis [9].

ACE-I have been demonstrated to increase arterial dilation via bradykinin B_2 receptor-dependent activation of nitric oxide production [10], and they improve endothelial dysfunction [7]. Increases in bradykinin levels are also associated with increased availability of prostacyclin and endothelium-derived hyperpolarizing factor, both of which are vasodilatory. As a result, ACE-I lower arteriolar resistance and increase venous capacity, increase cardiac output and cardiac index, stroke work and volume, lower renovascular resistance, and are able to maintain a neutral sodium balance state.

ACE-I are included in the initial drug choices for the management of hypertension based on their proven efficacy in lowering BP in a broad range of patients [2]. In addition, ACE-I are one of the preferred agents for the management of diabetic kidney disease and non-diabetic kidney diseases with albuminuria/proteinuria. In these diseases, they lower BP, reduce proteinuria, slow the progression of kidney disease, forestall development of end-stage renal disease (ESRD), and likely reduce cardiovascular (CV) disease risk by mechanisms above and beyond the lowering of BP [6].

In addition to their role in managing hypertension, CV, and renal disease, ACE-I are also used for primary and secondary prevention of CV events. Initial data demonstrating the efficacy of ACE-I for the prevention of CV events was found in the Heart Outcomes Prevention Evaluation (HOPE) trial in which the use of ramipril compared with placebo reduced a variety of CV disease events in individuals with prior CV disease or diabetes mellitus [11].

IMPORTANCE OF THE RENIN-ANGIOTENSIN SYSTEM IN MEDIATING BLOOD PRESSURE AND RISK FOR HYPERTENSION

The renin-angiotensin system (RAS) is activated in response to hypotension and plays an important role in regulating arterial pressure and extracellular fluid volume [9]. The RAS system is also activated in response to decreased serum sodium concentrations in the distal tubule, decreased blood volume, and renal sympathetic nerve stimulation. In such a situation, the kidneys release renin, an enzyme that hydrolyzes hepatically-derived angiotensinogen into angiotensin I. Angiotensinogen can also be produced by insulin resistant visceral adipose tissue. Angiotensin I is then converted to angiotensin II via ACE in the pulmonary

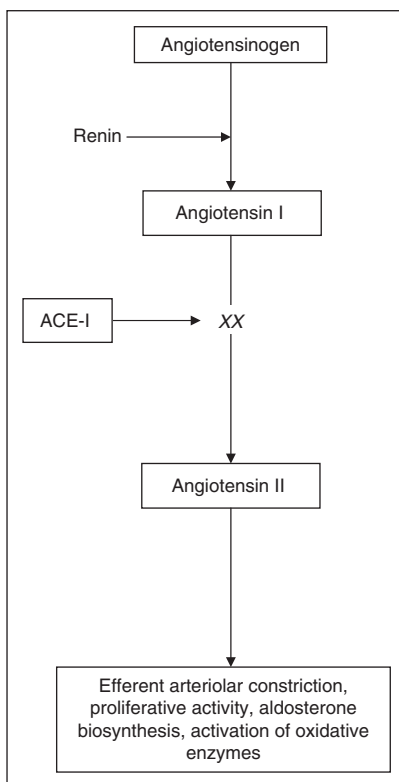


Figure 6.1 Physiology of the renin-angiotensin system and site of action of ACE inhibitors.

circulation as well as in the vascular endothelium [12]. ACE-I specifically inhibit the formation of angiotensin II and prevent the proteolytic degradation of bradykinin. This accumulation of bradykinin is one of the putative mechanisms by which ACE-I induce cough [13–15].

There is increasing evidence that ACE-I, through inhibition of the RAS, provides end-organ protection [9]. The dual roles of the RAS in salt and water homeostasis and the vascular response to injury have been linked to end-organ damage, which results from endothelial dysfunction, elevated BP, increased oxidative and inflammatory stress, and abnormal tissue remodeling and fibrosis [9].

As blockade of the RAS has been shown to prolong survival and reduce adverse outcomes in patients with systolic HF [16, 17] or left ventricular systolic dysfunction, [18–23] they have become the cornerstone of treatment in the management of hypertension, HF, diabetes, chronic kidney disease (CKD) and MI [24].

A number of ACE-I are used in clinical practice, with 10 currently in use in the United States (Table 6.2). All ACE-I decrease the activity of ACE; however, their chemical composition and structure vary and they have different rates of absorption, protein binding, half-life, and metabolic disposition (Table 6.3) [13, 25].

ACE-I CLINICAL TRIALS

An impressive number of clinical trials have demonstrated the efficacy of ACE-I in the management of hypertension as well as in reducing CV and renal morbidity and mortality in

Table 6.2 ACE inhibitor agents

■	Benazepril (Lotensin)
■	Captopril (Capoten)
■	Enalapril (Vasotec)
■	Fosinopril (Monopril)
■	Lisinopril (Prinivil, Zestril)
■	Moexipril (Univasc)
■	Perindopril (Aceon)
■	Quinapril (Accupril)
■	Ramipril (Altace)
■	Trandolapril (Mavik)

high-risk patients beyond lowering BP (Table 6.4) [26]. One of the first studies assessing the effect of ACE-I on end-organ function was undertaken by the Collaborative Study group, which found that captopril 25 mg thrice daily significantly reduced loss of renal function in 409 patients with type 1 diabetes mellitus compared with placebo [27].

In the HOPE study, 9297 high-risk patients (55 years of age or older) who had evidence of vascular disease or diabetes mellitus and a CV risk factor were randomized to ramipril (10 mg qd) or placebo for a mean of 5 years [11]. The primary outcome was a composite of MI, stroke, or death from CV causes. Ramipril was found to reduce the rates of CV death compared with placebo (relative risk, 0.74; $P < 0.001$), MI (9.9% *vs* 12.3%; relative risk, 0.80; $P < 0.001$), stroke (3.4% *vs* 4.9%; relative risk, 0.68; $P < 0.001$), death from any cause (10.4% *vs* 12.2%; relative risk, 0.84; $P = 0.005$), revascularization procedures (16.0% *vs* 18.3%; relative risk, 0.85; $P = 0.002$), cardiac arrest (0.8% *vs* 1.3%; relative risk, 0.63; $P = 0.03$), HF (9.0% *vs* 11.5%; relative risk, 0.77; $P < 0.001$), and complications related to diabetes mellitus (6.4% *vs* 7.6%; relative risk, 0.84; $P = 0.03$). The HOPE trial demonstrated the benefit of ACE-I in secondary prevention in a wide range of CV diseases including diabetes mellitus and vascular disease.

In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), 6105 patients with a history of stroke or transient ischemic attack with and without hypertension were randomized to perindopril (4 mg/day) with the addition of the diuretic indapamide as clinically indicated compared with placebo [28]. Over a mean of 3.9 years of follow-up, active treatment reduced blood pressure by 9/4 mmHg compared with placebo and reduced the primary outcome of stroke by 28%. Active treatment reduced the risk of major coronary events by 26% (95% CI 6–42%; $P = 0.02$) and the risk of HF by 26% (5–42%; $P = 0.02$). There were no differences in outcomes in subjects classified as hypertensive or non-hypertensive, and those with or without a history of coronary heart disease, further demonstrating the benefit of ACE-I in both CVD patients with and without hypertension.

The Avoiding Cardiovascular Events in COMbination Therapy in Patients LIVING with Systolic Hypertension (ACCOMPLISH) study examined the use of combination antihypertensive treatment with benazepril plus the calcium channel blocker (CCB) amlodipine compared with combination treatment with benazepril plus the thiazide diuretic hydrochlorothiazide (HCTZ) in 11 454 high-risk patients with hypertension [29]. Sixty percent of patients had diabetes mellitus, 46% had a history of prior CV (e.g. acute coronary syndrome, coronary artery bypass graft, or percutaneous coronary intervention), and 13% had a history of stroke. The study was stopped early, as the results demonstrated that combination therapy with benazepril and amlodipine had a 20% lower risk of major CV events. As many patients with hypertension required combination drug therapy to achieve target goals, the ACCOMPLISH study provides further evidence of the benefit of using ACE-I in combination therapy regimens, especially with a CCB.

Table 6.3 Comparison of angiotensin-converting enzyme inhibitors dosing and pharmacologic properties (adapted with permission from [2, 13, 14])

<i>Drug</i>	<i>Usual dose range in mg/day</i>	<i>Usual daily frequency</i>	<i>Onset/duration (hrs)</i>	<i>Peak hypotensive effect (hrs)</i>	<i>Protein binding (%)</i>	<i>Plasma half-life (hrs)</i>	<i>Elimination</i>
Benazepril	10–40	1	1/24	2–4	>95	10–11	Renal/ some biliary
Captopril	25–100	2	0.25/dose-related	1–1.5	25–30	<2	Renal as disulfides
Enalapril	5–40	1–2	1/24	4–6	50	11	Renal
Fosinopril	10–40	1	1/24	2–6	95	11	Renal = hepatic
Lisinopril	10–40	1	1/24	6	10	13	Renal
Moexipril	7.5–30	1	1/24	4–6	50	2–9	Renal/some biliary
Perindopril	4–8	1	1/24	3–7	10–20	3–10	Renal
Quinapril	10–80	1	1/24	2	97	2	Renal>hepatic
Ramipril	2.5–20	1	1–2/24	3–6	73	13–17	Renal
Trandolapril	1–4	1	2–4/24	6–8	80–94	16–24	Renal>hepatic

In the Studies Of Left Ventricular Dysfunction (SOLVD) trial, 2569 patients with HF (ejection fraction <35%; 90% New York Heart Association [NYHA] Class II and III) were randomized to enalapril at 2.5 to 20 mg/day compared with control [18]. A significant difference was found in mortality rates in patients taking enalapril ($P = 0.0036$). The largest reduction occurred in deaths attributed to progressive HF (risk reduction of 22%; 95% CI 6–35%). In addition, fewer patients died or were hospitalized for worsening HF (risk reduction of 26%; 95% CI 18–34%; $P < 0.0001$).

ACE-I TRIALS IN AMI

Several studies have assessed the efficacy of ACE-I use in acute MI (AMI). In the Acute Infarction Ramipril Efficacy (AIRE) trial, 2006 AMI patients with clinical evidence of HF were randomized to ramipril or placebo on day 3 to 10 after MI and followed for an average of 15 months [20]. Mortality rates were significantly lower for patients taking ramipril (170 deaths; 17%) compared with placebo (222 deaths; 23%). The observed risk reduction was 27% (95% CI 11–40%; $P = 0.002$). Analysis of secondary outcomes revealed a risk reduction of 19% for the first validated outcome (death, severe/resistant HF, MI, or stroke (95% CI 5–31%; $P = 0.008$).

In the Survival And Ventricular Enlargement (SAVE) trial, 2231 AMI patients (3 to 16 days post event) with ejection fractions <40 % were randomized to captopril or placebo for an average of 42 months. Significant reductions were found in patients receiving captopril compared with placebo with a 19% reduction in risk (95% CI 3–32%; $P = 0.019$) [19]. In addition fatal and non-fatal major CV events were reduced in the captopril group with a reduction in risk of 21% (95% CI 5–35%; $P = 0.014$) for death from CV causes, 37% (95% CI 20–50%; $P < 0.001$) for the development of severe HF, 22% (95% CI 4–37%; $P = 0.019$) for HF requiring hospitalization, and 25% (95% CI 5–40%; $P = 0.015$) for recurrent MI.

In the European trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA), 12 218 patients with MI (64%), angiographic evidence of CAD

Table 6.4 ACE inhibitor endpoint trials

<i>Trial</i>	<i>Patients</i>	<i>ACE-I</i>	<i>Risk reduction</i>
HOPE	9297 vascular disease or diabetes	Ramipril	20% in MI, 26% in CV death 32% in stroke
AIRE	2006 AMI with heart failure	Ramipril	27% mortality, 19% for subsequent event (death, heart failure, stroke, AMI)
PROGRESS	6105 HTN and non-HTN with history of CVA	Perindopril	26% in risk of major coronary event or CHF
ACCOMPLISH	11 454 High risk HTN	Benazepril in combination with amlodipine	20% in CV death, fatal/non-fatal AMI, fatal/non-fatal stroke, unstable angina coronary revascularization
SOLVD	2569 CHF (EF <35%)	Enalapril	16% in CV mortality, 26% CHF death or re-hospitalization
SAVE	2231 AMI (EF <40%)	Captopril	19% in mortality, 21% CV death, 37% severe CHF, 22% CHF requiring hospitalization, 25% recurrent AMI
EUROPA	12 218 AMI CAD, coronary revascularization	Perindopril	20% in CV death, AMI or cardiac arrest
TRACE	1749 AMI (EF <35%)	Trandolapril	22% in mortality, 25% CV death, 29% in progression to severe heart failure
CONSENSUS II	6090 AMI	Enalapril	No significant differences in mortality compared with placebo
SMILE	1556 AMI	Zofenopril	25% in death, 46% for severe CHF, 29% in 1-year mortality rates
QUIET	1750 ischemic heart disease	Quinapril	No significant difference in ischemic events (CV death, AMI, CABG, coronary angioplasty, resuscitated cardiac arrest, hospitalization for angina pectoris)
CCS-1	13 634 AMI	Captopril	Captopril was associated with a non-significant reduction in 4-week mortality ($P = 0.3$)

ISIS-4	58 050 AMI	Captopril compared to mononitrate and intravenous magnesium sulphate for 1 month	Captopril was associated with 7% reduction (4-9 fewer deaths) per 1000 patients treated
GISSI-3	19 394 AMI	Lisinopril	Lisinopril was associated with a 11% lower risk of death
VALIANT	14 703 AMI	Captopril compared to valsartan	No differences in CV death, recurrent AMI or CHF re-hospitalization
ONTARGET	2835 HTN	Ramipril compared to telmisartan	No differences in CV death, AMI, stroke, or CHF re-hospitalization
ACCOMPLISH = Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension; AIRE = Acute Infarction Ramipril Efficacy; AMI= acute myocardial infarction, CABG = coronary artery bypass graft surgery CAD = coronary artery disease; CCS = Chinese Cardiac Study; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; CVA= Cerebrovascular accident; EF = Ejection Fraction; EUROPA = European trial on Reduction of Cardiac events with Perindopril in Stable Coronary Artery Disease; GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto miocardico; HOPE = Heart Outcomes Prevention Evaluation; HTN = hypertension; ISIS = International Study of Infarct Survival; LVD = left ventricular dysfunction; ONTARGET = In The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; QUIET = Quinapril Ischemic Event Trial; SAVE = Survival And Ventricular Enlargement; SMILE = The Survival of Myocardial Infarction Long-Term Evaluation; SOLVD = Studies Of Left Ventricular Dysfunction; TRACE = Trandolapril Cardiac Evaluation; VALIANT = The Valsartan in Acute Myocardial Infarction.			

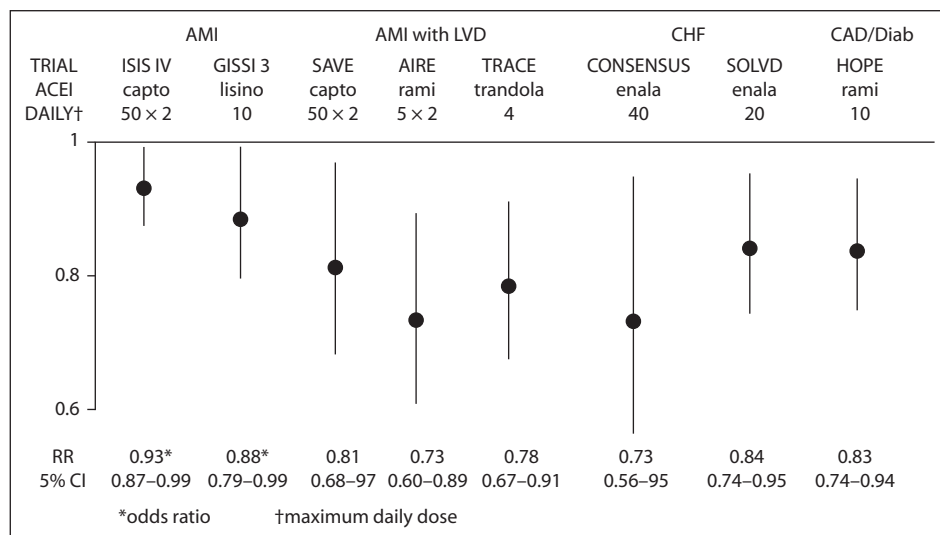


Figure 6.2 Mortality findings (relative risk +/- 95% confidence intervals) in ACE trials in patients with cardiovascular disease (with permission from [1]).

ACE-I = angiotensin-converting enzyme inhibitor; AIRE = Acute Infarction Ramipril Efficacy; AMI = acute myocardial infarction; CAD = coronary artery disease; CHF = congestive heart failure; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; Diab = diabetes; enala = enalapril; GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto miocardico; HOPE = Heart Outcomes Prevention Evaluation; ISIS = International Study of Infarct Survival; lisino = lisinopril; LVD = left ventricular dysfunction; SAVE = Survival And Ventricular Enlargement; SOLVD = Studies Of Left Ventricular Dysfunction; TRACE = Trandolapril Cardiac Evaluation.

(61%), history of coronary revascularization (55%), or a positive stress test only (5%) were randomized to perindopril (8 mg qd) or placebo [30]. The mean follow-up was 4.2 years. Treatment with perindopril demonstrated a 20% relative risk reduction (95% CI 9–29, $P = 0.0003$) in the composite primary outcome of CV death, MI, or cardiac arrest. The results from this large morbidity and mortality trial further demonstrated the benefit of ACE-I in CV disease risk reduction.

Several additional trials focusing on the use of ACE-I in AMI patients have further confirmed their pivotal role in the secondary prevention of CV disease. The Trandolapril Cardiac Evaluation (TRACE) trial randomized 1749 patients with MI and evidence of left ventricular systolic dysfunction (ejection fraction, <35%) to trandolapril or placebo. The duration of follow-up ranged from 24 to 50 months. The relative risk of death in the trandolapril group, as compared with the placebo group, was 0.78 (95% CI 0.67–0.91) [21]. Trandolapril also reduced the risk of death from CV causes (relative risk, 0.75; 95% CI 0.63–0.89; $P = 0.001$) and sudden death (relative risk, 0.76; 95% CI 0.59–0.98; $P = 0.03$) (Figure 6.2). In addition, progression to severe HF was less frequent in the trandolapril group (relative risk, 0.71; 95% CI 0.56–0.89; $P = 0.003$).

The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) study randomized 1556 anterior AMI after the onset of symptoms to zofenopril or placebo for 6 weeks. The incidence of death or severe congestive HF at 6 weeks was significantly reduced in the zofenopril group (reduction in risk was 46% [95% CI 11–71%; $P = 0.018$] and 25% (95% CI –11–60%; $P = 0.19$) for death compared with placebo [22]. After 1 year of observation, the

mortality rate was significantly lower in the zofenopril group (10.0%) than in the placebo group (14.1%), with a reduction in risk of 29 percent (95% CI 6–51%; $P = 0.011$).

Taken together, these trials evaluating the use of ACE-I in AMI demonstrate benefit for patients in reducing risk of CV death, MI and overall CV risk. While earlier clinical trials confirmed that ACE-I reduced CV events in patients with HF or left ventricular dysfunction, these trials focusing on the use of ACE-I in AMI have demonstrated the central role of ACE-I, including long-acting lipophilic ACE-I such as ramipril and perindopril, for reducing CV morbidity and mortality following myocardial injury.

ACE-I USE IN EARLY AMI

Several clinical trials have focused on the use of ACE-I in early AMI. In the Chinese Cardiac Study (CCS-1), 14 962 patients entering 650 Chinese hospitals up to 36 h (mean 16.6 ± 10.2 h) after AMI were randomized to captopril (6.25 mg initial dose, 12.5 mg 2 h later, and then 12.5 mg three times daily) or placebo for 4 weeks of therapy. Captopril was associated with a non-significant reduction in 4-week mortality ($P = 0.20$) [31]. Captopril was associated with a significant excess of hypotension, mostly after the start of treatment, with no evidence of any adverse effect on early mortality (16.3% captopril *vs* 10.8% placebo; 55 [SD 6] excess cases per 1000; $P < 0.0001$), mostly early after the start of treatment. No significant differences were demonstrated in the incidence of HF, cardiac arrest, or heart block.

The International Study of Infarct Survival (ISIS-4) compared the effects on mortality and morbidity of three treatments: 1 month of captopril (6.25mg initial dose titrated up to 50 mg twice daily) compared with matching placebo; 1 month of oral controlled-release mononitrate (30 mg initial dose titrated up to 60 mg once daily) versus matching placebo; and 24 h of intravenous magnesium sulphate (8 mmol initial bolus followed by 72 mmol) compared with control in 58 050 AMI patients [32]. There were no significant interactions between the effects of these three treatments. For patients treated with captopril, there was a significant 7% proportional reduction in 5-week mortality which corresponded to an absolute difference of 4.9 (SD 2.2) fewer deaths per 1000 patients treated for 1 month. Captopril was also associated with an increase in hypotension considered severe enough to require termination of study treatment, but having no effect on mortality on days 0–1, even among patients with low BP on entry to the study. There was no significant reduction in 5-week mortality with either mononitrate or magnesium sulphate therapy.

The Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto miocardico (GISSI-3) assessed the efficacy of 6 weeks of lisinopril (5 mg initial dose and then 10 mg daily) or control, transdermal glyceryl trinitrate 10 mg daily, and their combination in improving survival and ventricular function in 19 394 AMI patients [33]. Lisinopril, started within 24 h from onset of AMI symptoms, produced a significant reduction in mortality (11% lower risk of death) compared with controls. The administration of transdermal glyceryl trinitrate did not demonstrate a reduction in mortality; however, the combined administration of lisinopril and transdermal glyceryl trinitrate produced a significant 17% reduction in overall mortality.

The results of these trials of early ACE-I use in AMI indicate that such therapy is beneficial in reducing mortality. As demonstrated in these trials, the use of ACE-I in the early management of AMI is generally safe and typically prevents about 5 deaths per 1000 patients treated for the first month [31].

ADDITIONAL AMI ACE-I TRIALS

Not all ACE-I trials have demonstrated a significant benefit of treatment in AMI. In the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS II), 6090 AMI

patients were randomized to intravenous infusion of enalaprilat or placebo within 24 h after the onset of chest pain, followed by oral administration of enalapril [16]. There were no significant differences in mortality rates at either one or 6 months. The relative risk of death in the enalapril group was 1.10 (95% CI 0.93–1.29). Death due to progressive HF occurred in 104 patients (3.4%) in the placebo group and 132 (4.3%) in the enalapril group ($P = 0.06$). Therapy had to be changed because of worsening HF in 30% of the placebo group and 27% of the enalapril group ($P < 0.006$) [16].

In the Quinapril Ischemic Event Trial (QUIET), 1750 patients with ischemic heart disease without systolic left ventricular dysfunction were randomized to quinapril 20 mg/day or placebo and followed for a mean of 27 ± 0.3 months [34]. The 38% incidence of ischemic events was similar for both groups (relative risk 1.04; 95% CI 0.89–1.22; $P = 0.6$). There was also no significant difference in the incidence of patients having angiographic progression of coronary disease ($P = 0.71$) or in the rate of development of new coronary lesions ($P = 0.35$). Several study design limitations were present in QUIET including: an inadequate sample size, too short a follow-up, and too low a dose of quinapril, which complicate interpretation of the study results that failed to demonstrate a significant effect in the overall frequency of clinical outcomes or the progression of coronary atherosclerosis.

Results of the Prevention of Events with Angiotensin-Converting Enzyme Inhibition trial (PEACE) also demonstrated no significant CV benefit effect with ACE-I use (trandolapril 4-mg/day) in patients with CAD and preserved left ventricular function [35]. While there is accumulating evidence of the benefit of ACE in AMI and CVD, continued research is still needed to determine, which patient subgroups (including those with and without LV dysfunction) are best candidates for secondary prevention in CVD.

ACE-I AND ANGIOTENSIN RECEPTOR BLOCKADE (ARB) COMBINATION THERAPY

Several recent studies have demonstrated no differences in outcomes with ACE-I therapy compared to ARB blockade. The Valsartan in Acute Myocardial Infarction (VALIANT) trial compared captopril to valsartan in 14 703 AMI patients (0.5 to 10 days post) and found no differences in mortality, recurrent MI, or hospitalization for HF [36]. Therapy was begun with either 20 mg of valsartan, 20 mg of valsartan plus 6.25 mg of captopril, or 6.25 mg of captopril and doses were gradually increased to a goal of 80 mg of valsartan twice daily, 40 mg of valsartan twice daily and 25 mg of captopril three times daily, or 25 mg of captopril three times daily during the initial hospitalization and 160 mg of valsartan twice daily, 80 mg of valsartan twice daily and 50 mg of captopril three times daily, or 50 mg of captopril three times daily as tolerated by the 3-month visit. The proportion of patients taking the target doses were 56%, 47 %, and 56%, respectively ($P=0.97$ and $P<0.001$ for the two comparisons with the captopril group) [36]. The study results demonstrated that the ARB valsartan, at a target dose of 160 mg twice daily, was as effective as 50 mg of captopril three times daily in improving survival and reducing CV morbidity.

In The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), 17 620 patients with vascular disease or high-risk diabetes mellitus were randomized to 10 mg of ramipril per day, 80 mg of telmisartan per day, or combination therapy with both agents [37]. There were no differences in the primary composite outcomes of CV death, MI, stroke or MI, stroke, or hospitalization for HF among the three treatment groups. Combination therapy was associated with more adverse events (hypotension, syncope, and renal dysfunction) without increased benefit. The results of VALIANT and ONTARGET provide evidence that ACE-I and ARB are both beneficial in reducing CVD risk in patients with AMI, vascular disease or high-risk diabetes mellitus. However, combinations of ACE and ARB appear to confer no additional benefit beyond that observed with therapy with just one of these drugs, and may even incur harm under some circumstances as observed in the ONTARGET trial.

In reviewing the results of ACE-I clinical trials, there is sufficient clinical trial evidence confirming that ACE-I are important therapies in the treatment of AMI and CV disease, despite the fact that some studies have demonstrated no differences in outcomes. Overall, clinical trial evidence supports the effectiveness of ACE-I in AMI patients with markers of increased risk for mortality such as left ventricular dysfunction (SAVE, TRACE), symptoms of HF (AIRE), abnormal wall motion dynamics (SMILE), and for secondary prevention in HF or even (in the case of SOLVD and SAVE) in recurrent MI [8]. In addition, the results from several trials indicate that patients with CV disease may benefit from ACE-I treatment, independent of their level of left ventricular function.

Beginning with early studies evaluating the use of ACE-I in diabetes mellitus starting with the Collaborative Study Group [27], the benefit of ACE-I in hypertensive and non-hypertensive patients with any level of proteinuria in slowing the progression of renal disease is now well established. Other trials have confirmed the efficacy of ACE-I therapy for patients at risk of adverse CV events including HOPE and EUROPA, in which patients with coronary or other vascular disease or with diabetes mellitus and another CV risk factor treated with ACE-I had decreased CV disease-related mortality rates. An ongoing Cochrane review is comparing the effectiveness of ACE-I in patients with HF and will provide further information on the efficacy of ACE-I in CVD [38].

While review of these ACE-I clinical trials might indicate that ACE-I have equal benefit in the management of hypertension and CV disease, an issue of ongoing debate in the use of ACE-I is whether there is a class effect for all ACE-I when evaluating end-organ protection.

IS THERE A CLASS EFFECT OF ACE-I IN REDUCING CV MORBIDITY AND MORTALITY?

ACE-I are in a drug class defined by their specific mechanism of action within the RAS. While ACE-I have equal efficacy in the management of hypertension, they have wide ranging physiologic effects. The concept of a class effect is not well defined but relates to the assumption that all agents in a drug class are closely related in their mechanism of action, adverse effects, and pharmacologic profile [39]. Generally, agents within a class commonly demonstrate various pharmacologic effects and, therefore, drugs in a class should not be used interchangeably in the absence of evidence demonstrating comparability in long-term end-organ protection [40]. However, the use of ACE-I in clinical practice is often to substitute one for another. Managed care systems have certainly promoted this concept largely in an effort to reduce costs irrespective of whether or not evidence exists to support this practice.

A class effect might exist if the primary mechanism by which ACE-I impact CV risk is through their BP lowering effect [40]. However, ACE-I do differ in their ability to inhibit tissue ACE. *In vitro* studies have demonstrated that ACE-I such as ramipril and benazepril have high affinity for ACE, whereas enalapril and captopril have relatively low affinity for ACE, potentially indicating that even if the ACE-I can achieve equivalent BP control, they may not have equivalency with respect to inhibition of tissue ACE [40, 41].

While ACE-I similarly inhibit the activity of ACE, they have distinct chemical structures [1]. Captopril is a sulfhydryl-containing ACE-I, fosinopril is a phosphate containing ACE-I, and other ACE-I are dicarboxyl containing. Since they are not identical in chemical composition, the assumption that they are clinically interchangeable requires clinical evidence [1].

With respect to ACE-I, clinical trial evidence does not support the conclusion that their efficacy is interchangeable. Findings from the HOPE trial demonstrated the benefit of ramipril in reducing all-cause mortality (by 26%), AMI (by 20%), and stroke (by 32%) in patients with CV disease or diabetes mellitus and one CV risk factor. Additional evidence supporting the efficacy of ramipril was seen in the AIRE trial, where all-cause mortality was reduced by 27% in AMI patients with clinical evidence of HF. Yet other ACE-I clinical trials have demonstrated no effect on risk of CVD events including QUIET, which compared quinapril with placebo on risk of CV events including CV death, AMI, coronary artery bypass

grafting, coronary angioplasty, resuscitated cardiac arrest and hospitalization for angina pectoris in patients with ischemic heart disease, and CONSENSUS II, which found no differences comparing enalapril to placebo on mortality rates in AMI.

Further evidence against a class effect for ACE-I comes from animal model data demonstrating differential effects in therapeutic modulation of nitric oxide [42]. Positive modulation of endothelial nitric oxide synthase was found to be a class effect of ACE-I in the rat aortic endothelium among five different ACE-I (enalapril, perindopril, quinapril, ramipril, and trandolapril) at equipotensive doses, but the intensity of the modulation was found to vary with different ACE-I, with perindopril being the most effective [42].

However, a study of 16 068 AMI patients comparing the use of trandolapril, ramipril, enalapril, captopril, and perindopril found that different ACE-Is did have similar clinical efficacy in reducing mortality and recurrent AMI rates, suggesting a class effect among ACE-I when used in comparable doses [43]. Yet, the study was not a randomized design, did not assess the impact of ACE-I use in the early treatment of MI, and the dosages used were found to be below recommendations, with only 50% of average dosages at clinical guideline recommendations.

While ACE-I have been generally assumed to be equally effective in reducing CV risk, this has not been fully substantiated in clinical trial data. The clinical benefits of ACE-I do not solely reflect a class effect extending their benefit beyond BP-lowering effect. Despite the fact that there is data demonstrating event reduction with ACE-I in patients with HF or AMI, in the absence of comparative mortality and risk reduction data, evaluation of the equipotency of ACE-I is limited to the BP lowering effect [44]. Without prospective, randomized clinical trial data comparing the effects of different ACE-I at equipotent doses, it is difficult to draw conclusions on the question of whether or not ACE-I are equally effective in preventing clinical outcomes, such as preservation of renal function or ischemic events [1].

A recent Cochrane review of the BP lowering effect of ACE-I found no clinically meaningful BP lowering differences between different ACE-I [45]. The review evaluated 92 trials focusing on the dose-related trough BP lowering efficacy of ACE-I in 12 954 participants with a baseline BP of 157/101 mmHg. Comparisons of the data did not demonstrate that any one ACE-I was more effective at lowering BP. The results of the review indicated that the dose of 1/8 or 1/4 of the manufacturer's maximum recommended daily dose achieved a BP lowering effect that was 60 to 70% of the BP lowering effect of the recommended daily dose. In addition, a dose of 1/2 the maximum recommended daily dose achieved a BP lowering effect that was 90% of the recommended daily dose. Additionally, ACE-I doses above the maximum recommended daily dose did not significantly lower BP more than the recommended daily dose [45].

Despite the evidence that individual ACE-I achieve the same BP reduction, there is no evidence that they achieve the same degree of CV protection. The concept of a class effect for ACE-I is currently a hypothesis to be tested rather than an established principle guiding ACE-I therapy [40]. For use in clinical practice, it would therefore be best to utilize ACE-I therapy at doses in specific disease states as tested prospectively in clinical trials. A practical approach is to accept the assumption that the benefits of a particular ACE-I apply primarily to the investigated indication, doses, and outcomes [1]. It is difficult at best to argue for 'class effect' of ACE-Is as their therapeutic equivalency has not been fully demonstrated.

SUMMARY

Blockade of the RAS with ACE-I has been shown to positively impact survival and reduce adverse outcomes in patients with CV disease, including systolic HF, left ventricular systolic dysfunction, AMI, and diabetic and non-diabetic kidney disease. As a result, ACE-I have become a cornerstone in the treatment of patients with CV disease. Currently, however, there is insufficient data to establish a 'class effect' for ACE-I. Continued use and clinical trial

comparisons of ACE-I will provide additional data upon which to further evaluate the optimal, effective ACE-I therapy for CV disease treatment and prevention strategies.

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Are angiotensin-receptor blockers equivalent or superior to ACE inhibitors relative to blood pressure control and/or end-organ protection?

R. R. Townsend

BACKGROUND

As a chief resident in a teaching hospital in Pittsburgh in 1981–1982 it fell to that person to arrange the Medical Grand Rounds speakers for the year. Knowing captopril was being reviewed at the Food and Drug Administration (FDA) for approval in Spring of 1981 for the hypertension indication, arrangements were made to have Bernard Waeber from Hans Brunner's group in Lausanne, Switzerland (a group which had published several clinical papers on captopril) come to speak on the topic in September of 1981, about a month after captopril's approval for hypertension by the FDA in August. The two things I still remember almost three decades later from that 1 h talk was that 25 mg of captopril blocked a substantial portion of vascular angiotensin-converting enzyme (ACE) activity, and the pivotal role that the renin-angiotensin system (RAS) played in hypertension. At that time, therapy for hypertension consisted of rather large doses of thiazide diuretics (50–100 mg daily), α -methyl-DOPA or a β -blocker as a second step, and hydralazine as a third-line agent. Picture what the typical plasma renin activity (PRA) might be in a patient on 100 mg of hydrochlorothiazide (HCTZ) and 300 mg daily of hydralazine. Now imagine a starting dose of captopril in the range of 50–100 mg and you capture the setting of the perfect storm. When captopril therapy was initiated in the early 1980s it was not uncommon to be giving 450 mg or more a day.

In the early 1980s we used to admit some patients to the hospital who had severe hypertension and were starting captopril therapy because of the 'ACE crash' that would happen in a patient treated as outlined with diuretics and vasodilators (renin stimulating therapies) whose elevated blood pressure (BP) was attended by substantial activation of the RAS as witnessed by 100 mmHg drops in BP usually within 60 to 90 minutes of their first dose of captopril. Moreover, the original Capoten® package insert read like a chapter from a Stephen King novel, given the relegation to status as a fourth-line agent (i.e. not as initial therapy)

and the litany of serious adverse events associated with the product. Such adverse occurrences included a measles like rash, loss of taste, hyperkalemia, renal failure/proteinuria, and agranulocytosis. Add to the list angioedema, or 'angioneurotic edema' as it was called then, and it becomes clear why there was some hesitation in the early years to embracing ACE inhibition as a mainstream treatment for hypertension. Cough is not in this list as it was not until years later that cough was recognized to be an important side-effect of ACE inhibitor therapy.

However, the proof of concept was laid. Many patients tolerated captopril therapy quite well. Though hard to understand now, there was a recommendation to check the white blood cell count (for low granulocyte counts) and the urinalysis (for proteinuria) before refilling captopril prescriptions. Attention turned to the sulfhydryl group on captopril resulting from observations of the similarity of the side-effect profile of captopril to compounds like penicillamine [1]. This led to the development of non-sulfhydryl containing ACE inhibitors. The approval of the non-sulfhydryl containing ACE inhibitor enalapril in late 1985, its indication as initial therapy for hypertension, the recognition of the marked improvement in adverse event profile when captopril was limited to 300 mg daily, and the growing literature of the benefits of RAS blockade in heart failure (HF) established a solid niche for ACE inhibition in clinical medicine.

As ACE inhibition was more widely applied to clinical care side-effects soon became a not insignificant issue. The cough incidence, recognized as about three-fold higher than the background cough rate in the population studied, and the occasional occurrence of angioedema prompted the search for blockade of the RAS by other pharmacologic interventions. As a matter of reference, the background cough rate in the adult US population is 2–3% and with ACE inhibitor therapy the typical cough rate is 7–9% although these numbers are somewhat higher in females and blacks. In Hong Kong the background cough rate in adults is about 9%, and the ACE inhibitor associated cough rate is about 25–30%, which brought to bear an ethnicity component to cough rate. Angioedema rates have been reported to be less than 1% with ACE inhibition [2]. Though angioedema was initially thought to occur within the first week of ACE inhibitor therapy, it is now well established that it may occur even after years of ACE inhibition.

With the discovery of selective non-peptide blockers of the RAS, which focused on blockade of angiotensin II receptor binding sites, it became possible to block the RAS without ACE inhibitor side-effects such as cough. The FDA approved losartan for initial therapy in hypertension in 1995. Currently, there are ten ACE inhibitors and seven angiotensin-receptor blockers (ARBs) approved for multiple indications including hypertension, HF, diabetic nephropathy, left ventricular hypertrophy (LVH), and high cardiovascular risk.

IMPORTANT QUESTIONS

Fourteen years elapsed between the introduction of ACE inhibition in 1981 and the arrival of angiotensin-receptor blockade in 1995. Familiar landmark trials such as the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)[3], the Survival and Ventricular Enlargement (SAVE)[4], Study of Left Ventricular Dysfunction (SOLVD) [5], the Collaborative study of Angiotensin-Converting Enzyme Inhibition and Diabetic Nephropathy [6] and the Heart Outcomes Prevention Evaluation (HOPE)[7] established the value of ACE inhibitor therapy in randomized clinical trials. Other equally familiar trials such as Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL)[8] and the Irbesartan Diabetic Nephropathy Trial (IDNT)[9], the Losartan Intervention for Endpoints (LIFE)[10] and the various Candesartan in Heart Failure Assessment in Reduction of Mortality (CHARM) trials [11] established the value of angiotensin-receptor blockade in randomized clinical trials. Questions have risen repeatedly about the superiority of one or the other of these two widely used classes of cardiovascular agents. Recently, the Ongoing

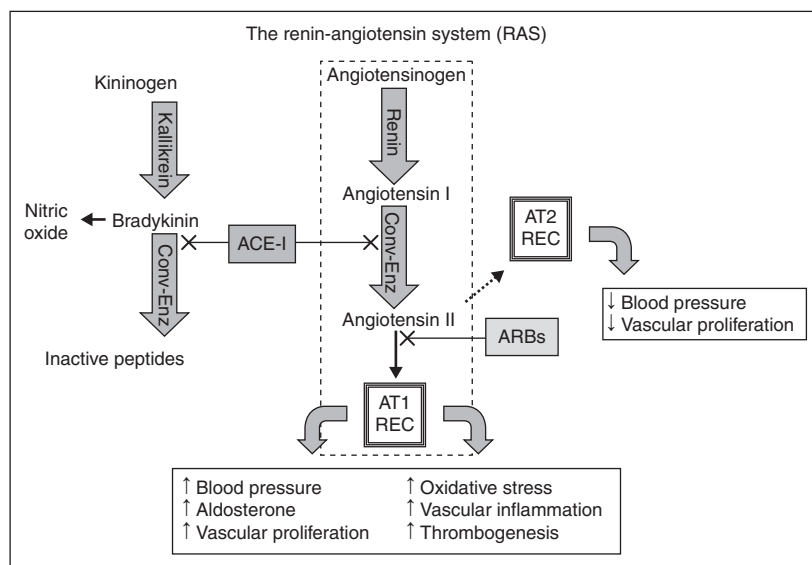


Figure 7.1 Outline of classical (within dashed-edge box) renin-angiotensin system (RAS) and points of RAS blockade with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. ‘Conv-Enz’ within arrows refers to angiotensin-converting enzyme in center of figure (which converts angiotensin I to angiotensin II) and to Kininase at left of figure (which converts bradykinin into inactive fragments). Small ‘x’ indicates sites of blockade of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs). ‘AT1 REC’ and ‘AT2 REC’ refer to angiotensin II receptors (subtypes 1 and 2). Dashed bold arrow indicates redirection of angiotensin II which increases during ARB therapy to the AT₂-receptor. Text boxes linked by curved arrows to angiotensin II receptors show the effects of receptor stimulation.

Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) [12] provided a very large head-to-head trial of ACE inhibition versus angiotensin-receptor blockade and allows a somewhat more informed discussion of this question. In addition, a number of smaller comparative trials have also approached this query in a variety of settings including hypertension as well as heart and kidney disease.

In this chapter four questions will be addressed:

- Are these two drug classes different in how they reduce blood pressure?
- Are these drug classes different in how they offer nephroprotection?
- Are these drug classes different in how they offer cardioprotection?
- Is the side-effect profile different between ACE inhibitors and ARBs?

QUESTION 1: ARE THESE TWO DRUG CLASSES DIFFERENT IN HOW THEY REDUCE BLOOD PRESSURE?

The simple answer is an unqualified “*probably.*” In Figure 7.1, details of the antihypertensive mechanisms of action of ACE inhibition and angiotensin receptor blockade are outlined, with the classic pathway indicated by the dashed-edge box encasing the center of the figure. However, there are several other aspects to consider. Blocking ACE has other consequences besides a reduction in the generation of angiotensin II. Perhaps most noteworthy is the build-up of kinins such as bradykinin. The role of this accumulation of vasodilatory kinins

Table 7.1 Humoral responses to ACE inhibition or angiotensin receptor blockade

	<i>Plasma angiotensin II</i>	<i>Plasma renin activity</i>	<i>Bradykinin*</i>	<i>Plasma aldosterone</i>
ACE-inhibitor	↓	↑	↑	slightly↓ to neutral or ↑
ARB	↑	↑	↔	slightly↓ to neutral or ↑
*Bradykinin here refers to vasodilatory effects; it is difficult to assay in plasma/serum				

was evaluated by a short-term study in which salt depleted people (both hypertensive and normotensive) were given captopril alone, or captopril with the bradykinin receptor antagonist icatibant (HOE 140). The co-administration of icatibant lessened by about half the BP reduction achieved with captopril alone [13]. In a related experiment the vasodilatory effects of bradykinin infusion were not altered by the co-administration of losartan but were potentiated by the ACE inhibitor enalapril [14].

The downstream actions of RAS inhibition are predictable from inspection of Table 7.1, which provides a summary of the BP effects of various humoral mediators during ACE inhibition or angiotensin-receptor blockade.

A key difference shown in Table 7.1 is the effect of an ACE inhibitor versus an ARB on the plasma concentration of angiotensin II. Blockade of ACE produces a substantial fall in circulating angiotensin II in the short term. An equally substantive increase in levels of angiotensin II occurs when an ARB is given. When angiotensin II levels have been measured following ACE inhibitor therapy, not uncommonly they drift back toward pre-treatment levels despite continued administration of ACE inhibitors, a finding which argued for the generation of angiotensin II by non-ACE related pathways [15]. Moreover, the fall in serum aldosterone concentrations noted early in the course of ACE inhibition also drifts back toward pre-treatment levels. This 'escape' effect on aldosterone may be the result of a small but significant increase in potassium which would drive aldosterone secretion by a non-angiotensin II based mechanism [16].

The more focused AT₁-receptor antagonism with ARB therapy would argue for an better 'targeting' for RAS blockade. The principal benefit that might emerge with this approach would be an improvement in side-effect profile (see question 4 below). An interesting twist in the ARB story occurred in the early 1990s when many of us were engaged in the phase II/III trials of MK 954 (losartan). This was the discovery of a second angiotensin II receptor (now known as the AT₂-receptor) whose function was unknown at that time. The increase in plasma concentrations of angiotensin II with ARB therapy would be expected to provide the AT₂-receptor with greater amounts of ligand. Fortunately, the effects of AT₂-receptor stimulation have generally been salutary (see Figure 7.1); thus, the initial concerns about AT₂-receptor stimulation have been laid to rest at the current time.

QUESTION 2: ARE THESE DRUG CLASSES DIFFERENT IN HOW THEY OFFER NEPHROPROTECTION?

Nephroprotection (also called renoprotection) is an often used yet infrequently defined term. Simple semantics would restrict its usage to protecting kidney function. However, inextricably bound up with preserving kidney function is the effect of agents on urinary albumin and total protein excretion. Consequently, included in this section are comparisons of ACE inhibitors and ARBs for both preserving kidney function and reducing urinary protein losses.

Table 7.2 Summary of trials comparing ACE inhibitor and ARB treatment on proteinuria

	<i>ARB</i>	<i>ACE inhibitor</i>	<i>Ratio of means: ARB/ACE inhibitor*</i>	<i>CI (95%)</i>
Proteinuria reduction [17]				
1–4 months Rx	<i>n</i> = 638	<i>n</i> = 634	0.99	0.92–1.05
5–12 months Rx	<i>n</i> = 429	<i>n</i> = 430	1.08	0.96–1.22
*See text for details				

The first study of RAS interruption which demonstrated preserved kidney function compared captopril with placebo in participants with type 1 diabetes mellitus and baseline proteinuria exceeding 500 mg daily [6]. Nearly a decade later two studies confirmed the ability of RAS blockade with either the ARB losartan or irbesartan to reduce the likelihood of renal function loss in type 2 diabetes mellitus with similar degrees of proteinuria as in the type 1 diabetic nephropathy study with captopril [8, 9]. The main BP-independent mechanism proposed for the benefit of RAS blockade in preserving kidney function has been that of a selective reduction in capillary pressures by way of vasodilation of post-glomerular efferent arterioles; although, some have argued that a regional increase in bradykinin with an ACE inhibitor might be an added benefit when compared with an ARB.

Proteinuria

A recent summary of head-to-head trials comparing ACE inhibitor treatment with ARB therapy on the endpoint of reducing proteinuria (Table 7.2) showed similar antiproteinuric effects with both drug classes. The “*ratio of means*” reported in Table 7.2 is a comparison of the magnitude of protein reduction in the ACE inhibitor/ARB treated participants in the reported trials. The antiproteinuric effect of ACE inhibitor or ARB treatment is about the same irrespective of the level of proteinuria or the underlying renal disease, and whether the effect is evaluated in short (less than 5 months) or longer-term studies.

Renal function in those without diabetes mellitus

Unlike the case with proteinuria, there are few head to head comparisons of an ACE inhibitor compared with an ARB based regimen where change in kidney function *per se* is the sought after outcome. A Japanese study randomly assigned patients with CKD (mostly glomerulonephritis and hypertension) to an ACE inhibitor regimen (trandolapril or benazepril; *n* = 36) compared with an ARB regimen (candesartan or losartan; *n* = 32) and followed them for 5 years [18]. Blood pressure control was similar in the two groups, but, after the third year of follow-up, those on the ACE inhibitor treatment had less end-stage renal disease compared with those on ARB therapy. In this study the ARB group started with a lower estimated glomerular filtration rate (eGFR) of 38 compared with 44 ml/min/1.73m² and higher urinary protein excretion (2.6 compared with 2.1 g/day), which might have favored the ACE inhibitor arm, although the differences at baseline were not considered statistically significant.

Renal function in those with diabetes mellitus

Barnett *et al* randomized 250 type 2 diabetics, 120 to telmisartan 80 mg daily and 130 to enalapril 20 mg daily and followed them for 5 years in the Diabetics Exposed to Telmisartan and Enalapril (DETAIL) study [19]. The primary outcome was the change in the glomerular

filtration rate (which was determined by the plasma clearance of iohexol). They found that change in the glomerular filtration rate (GFR) was $-17.9 \text{ ml/min/1.73 m}^2$ in those randomized to telmisartan as compared with $-14.9 \text{ ml/min/1.73 m}^2$ in those randomized to enalapril. The 95% confidence interval in the *differences* in eGFR between the two treatments was -7.6 to $+1.6 \text{ ml/min/1.73 m}^2$ (so the differences were not considered statistically significant). As with the Japanese study in CKD not due to diabetes mellitus, the effects on kidney function were a little more salutary with the ACE inhibitor compared with the ARB. Unlike the Japanese study, the eGFR at the time of enrollment in the Barnett study was $91 \text{ ml/min/1.73 m}^2$ (a creatinine of $>1.6 \text{ mg/dl}$ or an eGFR $< 70 \text{ ml/min/1.73 m}^2$ were prespecified exclusions). In the DETAIL study the BP, particularly the diastolic component, appeared to be lower on the ACE inhibitor treatment, but this was not specifically addressed by the investigators.

Renal outcomes in the ONTARGET trial

In the summer of 2008 renal outcomes of the large ONTARGET clinical trial were published [20]. Composite kidney outcomes were a prespecified endpoint in the trial and included receiving dialysis, doubling of serum creatinine, and death. The investigators also evaluated changes in eGFR and proteinuria.

The number of composite kidney outcomes was similar for the 8542 subjects assigned to telmisartan ($n = 1147$ or 13.4% had the outcome) and the 8576 subjects assigned ramipril ($n = 1150$ or 13.5% had the outcome). The hazard ratio comparing the kidney outcome between the two drugs was 1.00 [0.92–1.09]. The kidney outcome occurrence when death was *not* in the composite was similar with telmisartan therapy (189 [2.21%]) compared with ramipril ($n = 174$ or 2.03%; HR 1.09, [0.89–1.34]). Estimated GFR declined less with ramipril compared with telmisartan ($-2.82 + 17.2 \text{ (SD) ml/min/1.73 m}^2$ compared with $-4.12 + (17.4) \text{ ml/min/1.73 m}^2$; $P < 0.0001$). Urinary albumin excretion increased over time in patients assigned either the ACE inhibitor ramipril or the ARB telmisartan. The increase in urinary albumin excretion was less with telmisartan than with ramipril ($P = 0.004$).

Kidney transplantation

This was added because there are so few head-to-head comparisons between ACE inhibitors and ARBs in the area of kidney transplantation. A systematic review in 2007 found that use of an ACE inhibitor or an ARB in kidney transplant recipients resulted in a lower estimated GFR (by about 6 ml/min at 1 year) when compared with either placebo or non-RAS blocking therapy, consistent with the known effects of both of these drug classes to reduce hyperfiltration [21]. This review did not compare the RAS blocking agent classes head to head (there were only 4 trials from all reviewed, which compared these two drug classes within the same study and these were specifically excluded) [21]. Limited short-term prospective data suggests no difference in antiproteinuric effect between ACE inhibition (enalapril; 25 patients) and ARB (losartan; 12 patients) therapy in transplant patients, although a modest but statistically significantly greater reduction in creatinine clearance was noted on the ARB (11 ml/min) compared with the ACE inhibitor (6 ml/min) after 1 year [22].

QUESTION 3: ARE THESE DRUG CLASSES DIFFERENT IN HOW THEY OFFER CARDIOPROTECTION?

Included in this section are comparisons of ACE inhibitors and ARBs for myocardial infarction, HF, stroke, and cardiovascular (CV) or any death. As with Question 2 the premise(s) for why there may be differences in outcomes between these two classes of medication should be explored.

Table 7.3 Cardiovascular outcomes on ACE inhibitors compared with ARB therapy (adapted with permission from [26])

	<i>ARBs</i> (<i>n</i> = 18 245)	<i>ACE inhibitors</i> (<i>n</i> = 18 292)	<i>Odds ratio</i> (<i>ARB vs ACE</i>)	<i>95% CI</i>
MI	1663	1628	1.01	(0.95–1.07)
Stroke	717	768	0.93	(0.84–1.03)
CD death	2090	2021	1.04	(0.97–1.11)
Any death	2770	2707	1.03	(0.97–1.09)
CD = cardiovascular disease; MI = myocardial infarction.				

It has been suggested that some of the protective effects of ACE inhibitors on coronary artery disease may be independent of the degree to which BP is reduced [23]. In particular, some have argued that the increase in bradykinin occurring with ACE inhibitor treatment, and not so much so with ARB therapy, might bring to bear specific cardioprotective effects [24]. On the basis of concepts like these, a recent review of selected trials indicated that ARBs reduce the risk of MI to a lesser degree than that obtained with other antihypertensive drugs [25]. Long-term binding of angiotensin II type 2 (AT₂) receptors by increased serum levels of angiotensin II associated with long-term selective blockade of angiotensin II type 1 (AT₁) receptors might trigger a cascade of events, including: apoptosis, impaired angiogenesis, diminished synthesis of fibrotic tissue, decreased myocardial angiogenesis and growth of collateral vessels in the setting of ischemia, and reduced collagen content and fibrous cap thickness in atherosclerotic plaques possibly leading to increased risk of plaque rupture [26]. Finally, stimulation of AT₂ receptors could protect cerebrovascular function by actually recruiting collateral vessels and enhancing resistance of neurons to anoxia [27].

In 2008 several large systematic reviews incorporating many thousands of participants enrolled in prospective randomized clinical trials have enabled a comprehensive look into this question. One review appeared in early 2008 before the ONTARGET publication [28] and another later in 2008 incorporating the data from the ONTARGET trial [26].

The earlier review compared ACE inhibitors to ARBs for treating hypertension [28]. The authors chose studies lasting longer than 12 weeks and enrolling more than 20 participants. The most commonly used ACE inhibitor was enalapril and the most commonly used ARB was losartan. Among 47 randomized controlled trials there was no difference in BP control, lipid changes, and/or glycemic parameters using an ACE inhibitor compared with an ARB. In this review, there were too few CV outcomes for the authors to comment specifically on that issue.

In the later review [26], the ONTARGET results were included among the other randomized trials. This time there were 18 245 subjects on ARBs, who were compared with 18 292 subjects on ACE inhibitors. Table 7.3 shows the bottom line results.

The authors of this meta-analysis also compared ARB *plus* ACE inhibitor therapy to ARB therapy alone. The results were very similar to the above, except that there was a small further improvement in the stroke risk, which continued to favor the ARB, and reduced the odds ratio (OR) to 0.92 [0.85–0.99], which just achieved statistical significance. This subtle benefit of ARB on stroke risk may derive from AT₂-receptor stimulation as noted in animal models where the benefits of ARB protection on stroke are prevented by co-administration of AT₂-receptor blockers [27, 29]. Other proposed explanations for an ARB-related stroke benefit include reductions in platelet aggregability, reduced risk for new-onset type 2 diabetes mellitus, lower serum levels of uric acid (unique to losartan), and a benefit on atrial fibrillation-related stroke risk [30].

CV protection in the ONTARGET trial

The primary results of the ONTARGET were presented recently [12]. In this trial of more than 25 000 patients there were 8576 patients on ramipril 10 mg daily compared with 8542 participants on telmisartan 80 mg daily. After nearly 5 years of follow-up the primary composite outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for HF had occurred in 1412 patients in the ramipril group compared with 1423 patients in the telmisartan group (relative risk, 1.01 with a 95% confidence interval 0.94 to 1.09). Stroke, again, was somewhat lower in the ARB compared with the ACE inhibitor group, but the 95% confidence interval of the risk ratio (which was 0.91 [0.79–1.05]) crossed 1.0, rendering the results not statistically significant (of note, these results were a part of the analysis presented in Table 7.3).

QUESTION 4: IS THE SIDE-EFFECT PROFILE DIFFERENT BETWEEN ACE INHIBITORS AND ARBs?

The answer here is an unequivocal “yes”. The most commonly cited difference is cough. There is about a 3-fold higher incidence of cough with ACE inhibitor compared with ARB therapy [28]. The angioedema profile is much more prominent with ACE inhibitors, although package inserts for the ARBs do mention it as a rare occurrence as well [28].

The reductions in eGFR and the increases in serum potassium are comparable between the ACE inhibitor and ARB treatment, although one study showed somewhat less potassium elevation with the ARB (valsartan) compared with the ACE inhibitor (lisinopril) in patients with a GFR of 65 ± 5 ml/min/1.73 m² [31]. The ONTARGET trial noted a greater reduction in eGFR with the ARB telmisartan compared with the ACE inhibitor ramipril (see Question 2), and an even greater eGFR reduction when telmisartan was combined with ramipril [20].

In kidney transplant studies, there was either no difference in the frequency of hyperkalemia with an ARB compared with ACE inhibitor therapy after 1 year of treatment [22], or a slightly higher potassium level with ACE inhibitor (enalapril *vs* losartan) after 6 weeks of treatment [32].

For other side-effects such as headache and dizziness no significant differences in side-effect profiles of these two agent classes are apparent.

SUMMARY

Both ACE inhibitors and ARBs interfere with RAS activity, which is only one component of overall BP regulation. The means by which they do this, and some collateral effects on humoral mediators, are different. However, the overall magnitude of BP lowering is similar [28]. The cardiovascular benefits of the two drug classes appear similar with a modest tendency to more stroke reduction with ARB therapy. Their antiproteinuric effects are quite similar. Their respective benefits on kidney function protection from head-to-head outcome trials (except for ONTARGET) are sparse and it is difficult to state whether one class is superior to the other in preserving renal function. Available studies suggest that the decrements in estimated or measured GFR appear to be less with ACE inhibitor treatment, but the differences are small (on the order of 2 ml/min/1.73m² per year).

A few caveats are important to remember about ONTARGET. First is that a large number of participants enrolled in ONTARGET were already tolerating ACE inhibitor therapy, so the less than expected cough rate in the ramipril group (~4%) may be an underestimate. Although ONTARGET was a high cardiovascular risk study, there were relatively few subjects with microalbuminuria (about 13% in each of the ACE inhibitor and ARB arms) and patients with dipstick positive (macro) albuminuria represented about 4% of the subjects. The baseline eGFR in the ramipril and telmisartan groups of ONTARGET was about 74 ml/min/1.73m².

Finally, the side-effect profiles of ACE inhibitor and ARB are different, as known from about 25 years of clinical experience with ACE inhibitor and over 10 years of experience with ARBs. Cough and angioedema are much less frequent with ARB therapy and without a mechanistic basis.

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Treatment of hypertension in the post-stroke patient in both the acute and chronic setting

W. J. Elliott

BACKGROUND

Although elevated blood pressure (BP) is clearly a major risk factor for stroke [1, 2], and lowering BP may be the most effective way (from a population-based perspective) of preventing a first stroke [3], there is currently a great deal of controversy, at least in the United States, about whether BP-lowering should ever be considered (much less attempted or recommended) for a patient with a “stroke-in-evolution” [4, 5], and to what level the BP should be controlled once rehabilitation from the acute stroke has been completed [6, 7]. This chapter’s objective is to review the epidemiology, differential diagnosis, and treatment options for abnormal BPs after stroke, and conclude with an extended discussion of four of the most vexing questions in this clinical arena.

EPIDEMIOLOGY AND DIFFERENTIAL DIAGNOSIS OF ABNORMAL BP ACUTELY AFTER STROKE

Elevated BP (to $\geq 140/90$ mmHg) occurs in about 75% of patients presenting with an acute stroke. A systolic BP ≥ 180 mmHg is observed in about 60%, with a somewhat greater prevalence among individuals with prior hypertension, hemorrhagic stroke, and greater stroke severity. In the USA, about 87% of strokes are ischemic in origin, 10% are intracerebral hemorrhages, and about 3% are subarachnoid hemorrhages [8]. In most acute stroke patients with hypertension, the BP nearly always falls *without* intervention, during the first day to weeks, reflecting the fact that the elevated BPs are often attributable to other causes such as pain, distended bowel or bladder, psychological stress, physiological reaction to generalized or cerebral hypoxia, or increased intracerebral pressure (the “Cushing reflex”) [9]. A recent systematic review of 32 observational studies (that included more than 10 000 patients) concluded that, among all stroke patients, high systolic or diastolic BP (defined using various criteria in each study) was associated with a 1.5- to 5-fold increase in the risks of death, or the potentially more important composite of death or dependency [10, 11]. In another large database, every 10-mmHg elevation in systolic BP over 180 mmHg increased the risk of neurological deterioration by 40%, and the risk of a poor outcome by 23% [12]. Although hypertension is vastly more common in acute stroke patients, hypotension predicts a poor

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prognosis: in the same database: a BP <100/70 mmHg was associated with significantly poorer outcomes than a BP between 100/70 and 150/90 mmHg [13].

The differential diagnosis for hypotension in the face of an acute neurological event is important, because many of its underlying causes are reversible if treated. Thus, volume depletion (particularly in the setting of dysphagia), blood loss, decreased cardiac output due to myocardial ischemia, dysrhythmias (especially atrial fibrillation with a rapid ventricular response), and aortic dissection can all be improved, which generally leads to an improved neurological examination acutely and a better long-term prognosis. In general, a U-shaped curve is seen in the correlation of initial BPs and outcomes (all-cause mortality or the composite outcome of death or dependency) in ischemic stroke patients. For example, in the first International Stroke Trial, the best outcomes occurred among ischemic stroke patients with modestly raised or high-normal BP (optimum systolic BP around 150 mmHg). Higher BPs were independently associated with an increased risk of death from presumed cerebral edema, whereas lower BPs were associated with severe clinical stroke syndromes and an excess of deaths from coronary heart disease [12].

TREATMENT OPTIONS FOR ABNORMAL BP ACUTELY AFTER STROKE

There are many *theoretical* reasons why lowering elevated BPs in an acute stroke might be beneficial, including: reducing brain edema, reducing the risk of hemorrhagic transformation of an ischemic event, preventing further damage to blood vessels, and reducing the risk of early recurrent stroke. Very few, if any, of these have been demonstrated in large-scale clinical trials, perhaps because the traditional teaching in the USA has been that antihypertensive treatment is warranted in the acute phase of stroke ONLY if the BP is “*very high*” or the patient has another reason to mandate BP reduction (e.g., hypertensive encephalopathy, acute pulmonary edema, aortic dissection, etc.) [4]. Many older neurologists are very concerned about the risks of acute BP lowering, including worsening of the neurological defects because of decreasing perfusion pressure to watershed areas of the ischemic penumbra [4].

These fears were largely supported by the results of early trials of nimodipine (*vs* placebo) in acute stroke. As this drug had such beneficial effects in subarachnoid hemorrhage, it seemed reasonable to test its effects in other stroke subtypes. Unfortunately, no benefit of the drug was seen (in aggregate), and *post hoc* analyses showed poorer outcomes in nimodipine-treated patients with large infarcts and high pre-treatment BPs [13]. An analysis of 115 consecutive ischemic stroke patients found that each 10 mmHg reduction in systolic BP during the first 24 h was associated with an 89% increased risk of poor outcomes [14]. A subsequent report indicated that early lowering of systolic BP by >20 mmHg with nimodipine increased the risk of worsened neurological status early, and infarcted brain volume and death later on [11]. Because of the current focus of many neurologists on the early use of thrombolytic agents (which is typically contraindicated with BP >185/110 mmHg), current US stroke guidelines recommend antihypertensive therapy ONLY to achieve a BP that would allow intravenous thrombolytic therapy, or, otherwise, ONLY if the BP exceeds 180–230/105–120 mmHg [4]. The wide range of this threshold is evidence of the lack of general consensus on what to do about such BPs in the acute setting.

A number of uncontrolled or small trials have used ACE inhibitors, β -blockers, calcium antagonists, and nitrates in the acute stroke setting. Although few adverse effects have been reported, there seems to be little evidence of benefit, either [15]. A systematic review of cerebral blood flow and flow velocity in patients with acute ischemic stroke showed no major diminution in these parameters [16], but the consensus appears to be that the first 24 h after stroke onset is a window that antihypertensive therapy should not break [4].

Perhaps the most famous of the studies that began an antihypertensive agent AFTER the first 24 h of an acute ischemic stroke used candesartan, given at 4–16 mg/day, titrated to 32 mg/day (if BP >160/100 mmHg on day 2), and then other antihypertensive medications given as needed after the first week [17]. Ischemic stroke patients randomized to the “*control*”

arm received placebo for candesartan for the first week, and then candesartan 4–32 mg/day thereafter, followed by other antihypertensive drugs, as needed. This multicenter trial planned to enroll 500 patients, but accrual was discontinued after 339, because of a significant benefit of the early candesartan regimen on combined cardiovascular events (the difference in recurrent stroke was not significant: 13 of 173 *vs* 19 of 165). A small study saw lowered BPs and somewhat improved short-term stroke outcomes when ischemic stroke patients with elevated BPs were given either amlodipine or captopril, again beginning 24 h after stroke onset [18]. In contrast, bendrofluzide (the thiazide diuretic used most often in Great Britain) did not lower BP very well in a small British trial [19].

These data, taken together, demonstrate the therapeutic equipoise needed to launch clinical trials in which one group of hypertensive acute stroke victims could ethically receive relatively long-acting antihypertensive drugs, and the other could receive whatever “standard-of-care” regimen was in place at the time. The pilot phases of two such trials have recently been reported; neither showed an adverse effect of acute antihypertensive treatment, and therefore enrollment in the larger, definitive trial has been started in each case.

The INTensive blood pressure Reduction in Acute Cerebral hemorrhage Trial (INTERACT) was planned as a pilot study, with a primary endpoint of change in hematoma volume by computed tomography (a surrogate endpoint) at 24 h after randomization to either an intensive BP-lowering strategy (target systolic BP of 140 mmHg) or a “conventional treatment” group (target systolic BP of 180 mmHg) [20]. There were no restrictions on the drug (or drugs) used; most investigators in this Australasian trial used furosemide or urapadil as first-line agents. The intensively treated group had a 10.8 mmHg lower systolic BP (from 1–24 h after randomization), significantly smaller hematoma growth (13.7% *vs* 36.3%, $P = 0.04$) at 24 h, although this became non-significant after adjustment for several baseline variables. The authors extrapolated their observed difference in absolute hematoma size to about a 12% relative risk reduction for death or dependency. Only nine subjects suffered hypotension, and the “severe” form was actually more common in the “conventional” group. The authors therefore concluded that acute BP reduction in intracranial hemorrhage is feasible, well-tolerated, and worthy of study in a much larger trial (INTERACT-2).

In the pilot phase of the Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS) trial, 179 patients with acute ischemic or hemorrhagic strokes within the previous 36 h, who had systolic BP >160 mmHg were randomized to placebo ($n = 63$), labetalol ($n = 58$), or lisinopril ($n = 58$), the doses of which could be escalated for the first 2 weeks until the systolic BP was <150 mmHg [21]. For patients with dysphagia, intravenous or sublingual administration of agents was used. There were significant decreases in BP in the two actively treated groups during the first 24 h (–21 *vs* –11 mmHg), as well as at 2 weeks (–31 mmHg *vs* –24 mmHg). The primary endpoint, death or dependency at 14 days after stroke, did not differ significantly (61% *vs* 59%; $P = 0.82$). However, neither early deterioration nor adverse events was worse in the actively treated group; in fact, 3 months after treatment, the risk of death was more than halved (9.7% *vs* 20.3%; $P = 0.05$). These optimistic results (involving small numbers of subjects) will be tested further in a similar trial that will enroll 2050 subjects.

Several large, outcome-based trials of antihypertensive drugs for lowering BP during acute stroke are ongoing. The two largest of these include: the Continue or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS; 2900 patients with stroke, randomized to stop or continue pre-existing antihypertensive drugs for 2 weeks after stroke) [22], and the Efficacy of Nitric Oxide in Stroke Trial (ENOS; 5000 patients with stroke, randomized to transdermal nitroglycerine patch or not for 7 days after stroke onset) [23].

A very different approach has been advocated by other investigators, who believe that *increasing* BP will improve brain oxygenation and outcomes in the acute stroke patient. A retrospective review and a pilot study from the Massachusetts General Hospital suggested that 1–6 days of phenylephrine infusion, titrated to raise systolic BP by 20% (but not to exceed 200 mmHg), resulted in improved neurological status at hospital discharge [24].

Similarly, a comparison of 15 stroke patients with diffusion-perfusion mismatch on magnetic resonance imaging showed better National Institutes of Health (NIH) Stroke Scale scores, cognitive scores, and less hypoperfused brain tissue if they received drugs to mildly raise BP at presentation [25]. The most recent systematic review of this treatment option suggests that, although apparently safe and effective, the numbers of patients in the few small trials completed so far is insufficient to warrant a general recommendation for use [26], an opinion shared by the most recent American Stroke Association guidelines [4].

EPIDEMIOLOGY AND DIFFERENTIAL DIAGNOSIS FOR ABNORMAL BP WEEKS AFTER A STROKE

The amount and quality of clinical trial and epidemiological outcomes data improve as the amount of time between the acute stroke increases, prompting a different set of much more optimistic guidelines from the American Stroke Association [6]. As compared with primary prevention, fewer data exist between BP and secondary stroke prevention, but the direct relationship between BP and stroke risk still holds [27]. There are no formal surveys of the prevalence of hypertension or hypotension among long-term stroke survivors, but it is likely that hypertension should be more common in this than in the general population. As a result, the differential diagnosis of an abnormal BP in a stroke survivor is likely not different than what is considered in people without a stroke, except that other manifestations of atherosclerosis (including renovascular hypertension, as a potential cause of hypertension) are more likely. The evaluation of a stroke survivor with abnormal BP should likely follow the recommendations of JNC 7 [1], which typically has de-emphasized the role of extensive evaluations for secondary causes of hypertension unless there is a good clinical reason to do so (e.g. history of excessive dietary sodium consumption, presence of an abdominal bruit, unprovoked hypokalemia).

TREATMENT OPTIONS FOR ELEVATED BP WEEKS AFTER A STROKE

Although a large amount of clinical trial evidence suggests that antihypertensive drugs prevent stroke recurrence [28], and a number of the recent trials have suggested that the benefit is independent of the initial BP, there may well be differences in the effectiveness of different classes of antihypertensive drugs in secondary stroke prevention. Teasing out the data about secondary stroke prevention from many clinical trials is difficult, because subgroup analyses (reporting the numbers of patients who experienced **second** strokes) have not often been reported for trials that enrolled some, but not all, individuals who had suffered a first stroke. Fortunately, the Individual Data Analysis of Antihypertensive Intervention Trials (INDANA) investigators have gathered these data from trials completed prior to 1996 [29]; sadly, many recent, large and important trials, such as the Antihypertensive and Lipid-Lowering to prevent Heart Attack Trial, have not yet reported their data. The existing data [30–44] are summarized in Table 8.1. Unfortunately, a traditional Mantel-Haenszel meta-analysis (using a fixed-effects model) of the trials involving “*any active drug*” *vs* “*placebo/no treatment*” displays significant inhomogeneity ($P < 0.02$). Some of the inhomogeneity can be linked to the disagreement between the very positive overall results of the Perindopril Protection against recurrent Stroke Study (PROGRESS) [36], which showed a highly significant 26% reduction in recurrent stroke with perindopril $\pm$ indapamide *vs* placebo $\pm$ placebo, and the non-significant 6% reduction seen in the comparison of an ARB *vs* placebo in the larger Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial [39]. The results of a random-effects model (of DerSimonian and Laird [40]) are shown in Figure 8.1, the overall result of which is a significant reduction in recurrent stroke by 21% (95% confidence interval [CI] 0.58–0.92; $P < 0.002$). The inhomogeneity of this dataset is further illustrated in Figure 8.2, which shows the results of pairwise meta-analytic (direct) comparisons of the various initial antihypertensive drug classes used in these trials, including The Morbidity and

Table 8.1 Trials of chronic antihypertensive drugs in secondary stroke prevention

<i>Trial</i>	<i>Initial agent</i>	<i># of recurrent strokes/# at risk</i>	<i>Comparator</i>	<i># of recurrent strokes/# at risk</i>
Carter [30]	Diuretic	10/50	Placebo	21/49
HSCSG [31]	Diuretic	37/233	Placebo	42/219
EWPHÉ [29]	Diuretic	5/35	Placebo	9/28
Coope & Warrender [29]	β-blocker	2/11	No treatment	1/6
HDPF [29]	Diuretic	15/136	'Usual care'	16/138
SHEP [29]	Diuretic	8/59	Placebo	7/40
STOP-1 [29]	β-blocker (or diuretic)	1/31	Placebo	4/35
Dutch TIA [32]	β-blocker	52/732	Placebo	62/741
PATS [33]	Diuretic	159/2841	No treatment?	217/2824
TEST [34]	β-blocker	81/372	Placebo	75/384
HOPE [35]	ACE-I	43/500	Placebo	51/513
PROGRESS [36]	ACE-I (±diuretic)	307/3051	Placebo	420/3054
MOSES [37]	ARB	80/710	CCB	89/695
SCOPE [38]	ARB	6/97	Placebo	15/97
PROFESS [39]	ARB	880/10 146	Placebo	934/10 186

ACE-I = angiotensin converting enzyme-inhibitor; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; EWPHÉ = European Working Party on Hypertension in the Elderly; HDPF = Hypertension detection and follow-up program; SHEP = Systolic Hypertension in the Elderly Program; HOPE = Heart Outcomes Prevention Evaluation [35]; HSCSG = Hypertension-Stroke Cooperative Study Group [31]; MOSES = Morbidity and mortality after Stroke—Eprosartan vs. nitrendipine in Secondary prevention [37]; PATS = Post-stroke Antihypertensive Treatment Study [33]; PROFESS = Prevention Regimen For Effectively avoiding Second Strokes [39]; PROGRESS = Perindopril protection aGainst REcurrent Stroke Study [36]; SCOPE = Study on COgnition and Prognosis in the Elderly [38]; STOP-1 = Swedish Trial in Old Patients #1; TEST = [atenolol] Evaluation in Stroke Trial [34]; TIA = Transient Ischemic Attack [32].

Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES) [37]. In the aggregate, a diuretic or an ACE inhibitor showed significant benefit (compared with placebo) in preventing a second stroke, whereas neither a β-blocker nor an ARB was significantly better than placebo. Only one comparison involved a calcium channel blocker, and it was not significantly better in preventing the first recurrent stroke than the ARB, which was in turn not significantly better than placebo. Although there has not been a comparison of an ACE inhibitor *vs* a diuretic in secondary stroke prevention, their indirect comparison (each *vs* placebo) suggests they would not be much different (relative risk for the diuretic *vs* ACE inhibitor: 0.97, with 95% CI 0.73–1.21) [41]. Similarly, an indirect comparison of a diuretic *vs* ARB suggests superiority of the former (relative risk: 0.75, 95% CI 0.54–0.96).

The similarity of the effects of a β-blocker and placebo is seen, even without including the data of the Beta-blocker Evaluation in Stroke Trial (BEST), which reported only a larger number of deaths among subjects randomized to a β-blocker (*vs* placebo), and no information about recurrent strokes [42]. The paucity of trials comparing calcium channel blockers with any other treatment (active or placebo) greatly widens confidence intervals for both direct and indirect comparisons involving this class of drugs, and makes the results of “network

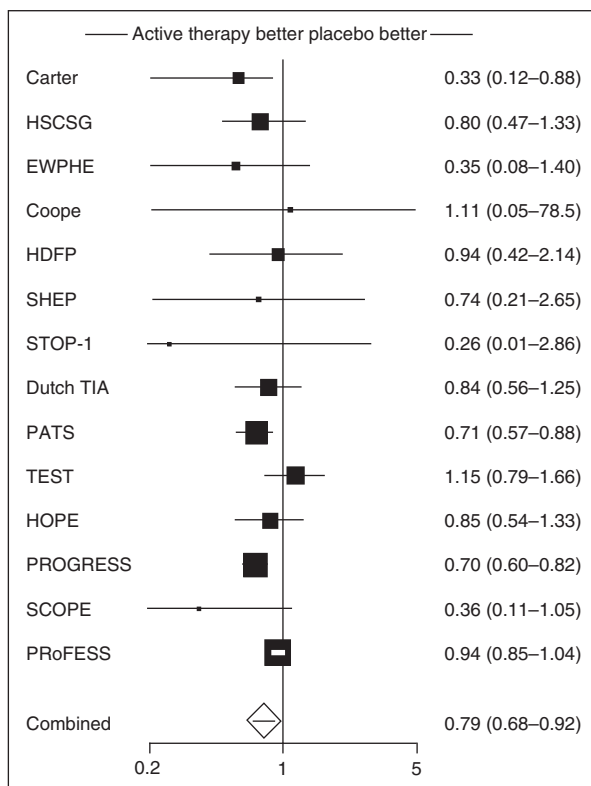


Figure 8.1 Results of a random-effects model meta-analysis of active antihypertensive agents vs placebo/no treatment in the prevention of a second fatal or non-fatal stroke. The overall pooled odds ratio for active treatment was 0.79, with a 95% confidence interval of 0.68–0.92, $P < 0.002$. As customary, the area of each ‘box’ (corresponding to the effect size) is inversely proportional to the variance of each trial; the horizontal lines correspond to the 95% confidence limits for the odds ratio for each trial. Acronyms of trials are expanded in the footnote to Table 8.1.

meta-analysis” of the secondary stroke data incoherent ($\omega = 1.65$) [43]. These conclusions, based on much more data than were available in 2006, echo the conclusions of the American Stroke Association: “*The optimal [antihypertensive] drug regimen remains uncertain*” [6].

What is less controversial is that chronic antihypertensive drug therapy, in the aggregate, can prevent recurrent stroke, and perhaps more importantly, major adverse cardiovascular events in patients with a history of cerebrovascular disease [2, 6, 7, 44]. In several of the recent trials, including PROGRESS [36], the Heart Outcomes Protection Evaluation (HOPE) [35], and the Study on Cognition and Prognosis in the Elderly (SCOPE) [38], the benefits were independent of the initial BP, and (in the aggregate) directly related to the difference in systolic BP between the randomized groups [44].

IMPORTANT QUESTIONS

WHAT SHOULD THE OPTIMAL BP BE FOR PATIENTS WITH AN EVOLVING STROKE?

As discussed above, the concept of attempting to control BP during the acute phase of a “*stroke-in-evolution*” is a relatively new one, and quite controversial [4, 5]. There have, to date,

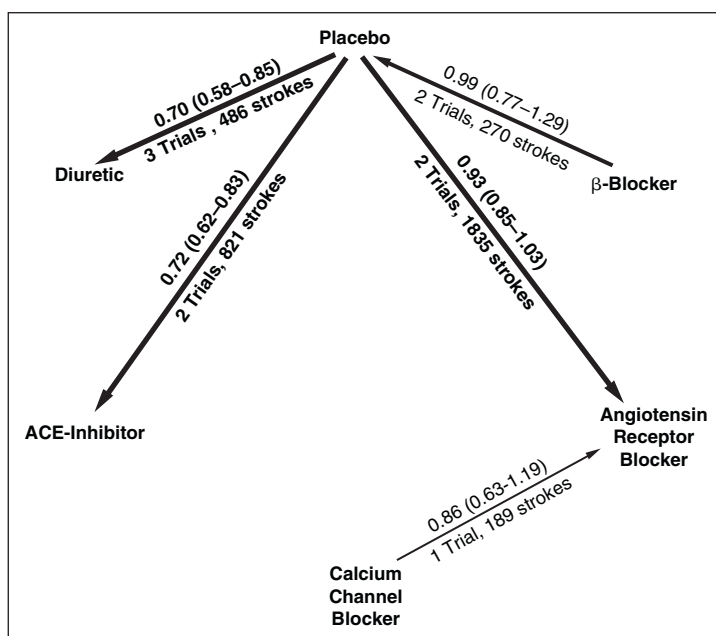


Figure 8.2 'Network' summarizing comparative trials involving placebo and/or different antihypertensive drug classes in clinical trials for prevention of recurrent stroke. The arrowhead between entries points to the drug class with the lower risk of recurrent stroke; the breadth of the line is proportional to the number of recurrent strokes in the pairwise meta-analytic comparison of the two entries. The summary odds ratio and its 95% confidence limits are shown above the line between each entry; the number of trials and recurrent strokes in each meta-analysis are shown below the line. Note that the 'network meta-analysis' of these data results in a large 'incoherence', presumably because of the limited number of studies comparing two active drug classes.

been no trials that have compared outcomes in groups of acute stroke patients randomized to achieve various levels of BP (as, for example was the intent in the Hypertension Optimal Treatment study). Current US guidelines, based primarily on experience and *post hoc* analyses of clinical trial and epidemiological data, suggest that physicians allow the BP in acute stroke patients to remain undisturbed unless the systolic BP exceeds 180 mmHg [4].

There are also no prospective randomized trials to determine the optimal BP for patients who are weeks removed from their acute stroke. Retrospective analyses of PROGRESS suggest that the lowest risk of stroke recurrence was seen in those in the lowest quartile of achieved BP (~112/72 mmHg), and rose progressively with higher follow-up BPs [44]. Rashid *et al.* have performed meta-regression analyses (see Figure 8.3 for an update), and concluded that there is a direct relationship between the relative risk reduction in recurrent stroke and the difference in achieved systolic BP between treatment arms [45]. These data are consistent with the general observation that higher risk patients do better with a lower target BP [1, 2], although the data specifically in patients with a history of cerebrovascular disease are similar to those in patients with established heart disease, but clearly weaker than those in diabetics or chronic kidney disease.

SHOULD BP EVER BE RAISED IN THE PATIENT WITH AN EVOLVING STROKE?

Current US guidelines recognize the high risk associated with hypotension in acute stroke patients [4], and acknowledge the importance of considering its differential diagnosis, par-

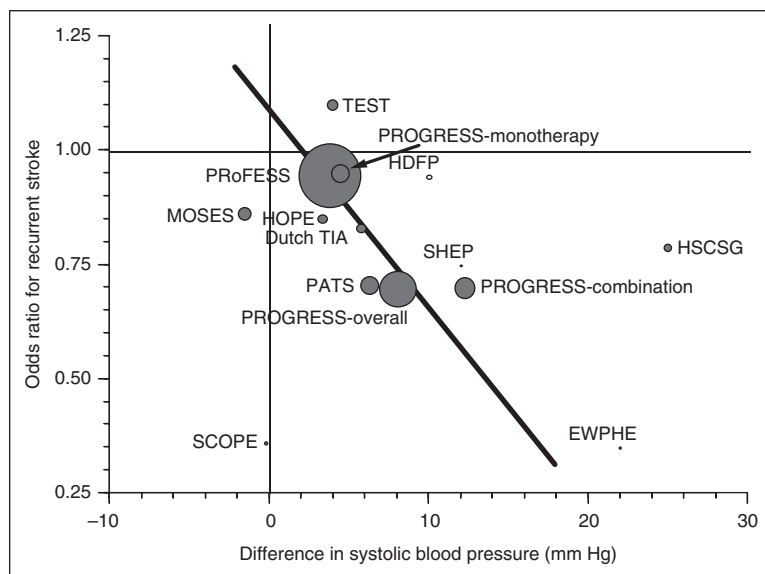


Figure 8.3 Plot of the significant relationship between the difference in systolic blood pressure between randomized arms during follow-up and the relative risk reduction for recurrent stroke in the clinical trials in Table 8.1. These data suggest that the larger the difference in achieved systolic BP, the greater the prevention of recurrent stroke. As is customary, the circle corresponding to each trial is drawn in proportion to the number of recurrent strokes observed. Trials that observed less than ten recurrent strokes have circles that are too small to see at the resolution of the figure. Acronyms of trials are expanded in the footnote to Table 8.1 (updated with permission from data in [45]).

ticularly since many of the possibilities are remediable. Thus, a patient with an evolving stroke who is volume depleted, suffering from an aortic dissection or cardiac ischemia, should have these conditions treated, which is likely to (secondarily) raise the BP. The idea of using short-acting vasoconstrictors (e.g. phenylephrine) in acute stroke patients appears to be meritorious in some, but more information is needed on how this can be done safely and be easily and quickly reversed if neurological deterioration or other adverse experiences occur [4, 24–26].

IS A SPECIFIC ANTIHYPERTENSIVE DRUG CLASS BETTER THAN OTHERS FOR THE SECONDARY PREVENTION OF STROKE?

As discussed above, the current clinical trials database is not extensive enough to allow clear or useful conclusions to be drawn from fixed-effects or network meta-analyses. It appears that β -blockers are not very effective to prevent recurrent stroke (and in the aggregate, were associated with a higher risk of death in three studies: BEST [42], Dutch Transient Ischemic Attack [TIA] [32] and The Evaluation in Stroke trial [TEST] [34]; relative risk 1.06; 95% CI 0.83–1.35; $P = 0.64$). Some would argue that the very large and statistically powerful PROGRESS trial clearly demonstrated that an ARB is not significantly better than placebo in preventing a second stroke. Based primarily on the PROGRESS results [36], the most recent US guidelines conclude that, “the available data support the use of diuretics and the combination of a diuretic and an ACE inhibitor (Class I, Level of Evidence A). The choice of specific drugs and targets should be individualized.”[4]

WHICH PATIENTS ARE AT RISK FOR POST-STROKE DEMENTIA?

Many epidemiological studies have attempted to identify risk factors for post-stroke dementia [46, 47]. The major ones include: younger age, pre-existing cognitive decline (without dementia), lower pre-stroke functional status, severity of the initial neurological deficit, presence of silent infarcts or cerebral atrophy on computed tomography (CT) or MRI done immediately after stroke [46].

The role of BP lowering and antihypertensive drugs in the prevention of dementia, with or without a preceding stroke, is controversial [48, 49]. The most recent meta-analysis of data from four trials involving 23 505 subjects showed a non-significant 20% (95% CI -2–37%; $P = 0.07$) relative risk reduction in dementia or cognitive decline in those randomized to active antihypertensive therapy [49]. The PROGRESS investigators reported a non-significant ($P = 0.20$) 12% reduction in dementia, but a significant decrease in cognitive decline (19%, $P = 0.01$), as well as the composite outcomes of recurrent stroke or dementia and recurrent stroke or cognitive decline [50]. These and other data do give many hope that “tight” control of BP may prevent not only recurrent stroke and major adverse cardiovascular events, but also dementia and cognitive decline.

SUMMARY

Treatment of hypertension in the acute post-stroke period is controversial. Current recommendations are to consider lowering BP only if the systolic exceeds 180 mmHg, although several recent trials have suggested that careful reduction in BP with long-acting antihypertensive agents, often after a short period of observation, may be beneficial. Other data indicate that raising BP in the acute stroke setting may be beneficial for some. Treatment of hypertension beginning in the weeks following an acute stroke is supported by data from a variety of clinical trials, although the largest and most recent of these did not have a significant result. In the aggregate, however, BP-lowering drugs appear to prevent recurrent stroke, and some data suggest that the greater the achieved BP difference between the two randomized groups, the better the prevention. Current US guidelines recommend a diuretic or a diuretic and an ACE inhibitor for the chronic treatment of hypertensive patients with a history of cerebrovascular disease. Whether such interventions decrease the incidence of dementia and/or cognitive decline is still uncertain.

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Isolated systolic hypertension and management of hypertension in the very elderly

S. S. Franklin

BACKGROUND

The natural history of hypertension has changed considerably since the invention of the auscultatory method of sphygmomanometric measurement of blood pressure (BP) in 1905. In the first half of the 20th century, adults in their forties or fifties presented with severe diastolic-systolic hypertension, frequently accelerated or malignant in nature, and associated with the rapid onset of cerebral hemorrhage, heart failure (HF) or end-stage renal disease (ESRD). This form of hypertension, unfortunately, still occurs, but with diminished frequency. More recently with the aging of our population and the advent of effective anti-hypertensive therapy, there has been a shift toward a more slowly progressive form of hypertension that is predominately systolic in nature, affecting middle-aged and older persons [1, 2]. This form of hypertension is frequently complicated by two separate types of cardiovascular (CV) events:

1. Longstanding comorbid atherosclerotic disease that results in coronary heart disease (CHD), thrombotic stroke and peripheral artery disease.
2. Microvascular disease that results in slowly progressive heart and renal failure as well as cerebral white matter lesions leading to cognitive impairment.

The misleading dictum of that previous era stated that a person's *normal* systolic blood pressure (SBP) was 100 plus their age. More recently, this slowly rising SBP with pathological aging is referred to as *isolated systolic hypertension* (ISH). Previously, ISH was defined as a SBP ≥ 160 mmHg and a diastolic blood pressure (DBP) of < 95 or < 90 mmHg. With the recognition of its true risk, ISH was redefined as a SBP ≥ 140 and DBP < 90 mmHg in the 1990s. The purpose of this chapter is to provide a better understanding of the hemodynamics, pathophysiology, etiology, epidemiology, and management of ISH.

HEMODYNAMICS OF ISH

The two major physiologic components of BP are mean arterial pressure (MAP) and pulse pressure (PP) [3]. MAP is simply the interaction of cardiac output (CO) and peripheral vas-

cular resistance (PVR), i.e. $MAP = CO \times PVR$. Pulse pressure depends on two major factors:

1. Left ventricular ejection characteristics.
2. The stiffness of the thoracic aorta.

The peak SBP and minimum DBP represent a weighted sum and difference of MAP and PP, respectively. PP in older subjects represents a surrogate measurement of central elastic artery stiffness in the presence of a constant CO and heart rate. Thus, central arterial stiffening becomes apparent by three interlinked factors: a rise in PP leading to a rise in SBP and a fall in DBP, ultimately resulting in ISH.

PERIPHERAL VASCULAR RESISTANCE AS A CV RISK FACTOR

Peripheral vascular resistance is determined by vessels $<300 \mu m$ in diameter, which include precapillary arterioles and small arteries [4]. The vessels of the microcirculation can increase resistance in three ways and in so doing raise BP. First, humoral and autonomic nervous system alterations in vasomotor tone and inherent myogenic tone (state of contraction of smooth muscle cells in vessel walls) can enhance vasoconstriction or reduce vasodilator responses. Second, there may be structural alterations in the intima and especially in the media that increase the wall-to-lumen ratio of precapillary resistance vessels (remodeling and hypertrophy). Lastly, there may be reversible or non-reversible rarefaction (reduction in the density) of arterioles and capillaries within a given vascular bed. Any one or a combination of two or three of these mechanisms can increase PVR and lead to impaired tissue perfusion, ischemia, and eventual target organ damage [5]. The equation for MAP is a surrogate measure of PVR. MAP (mmHg) is defined by $1/3 SBP + 2/3 DBP$. Therefore, increased DBP is always associated with increased PVR, but a normal or reduced DBP can be associated with increased PVR when there are large increases in SBP. In general, PVR is increased in proportion to the height of BP and has been considered the fundamental hemodynamic manifestation of essential hypertension.

LARGE ARTERY STIFFNESS AS A CV RISK FACTOR

Central arterial elasticity is critically dependent on normal content and function of the matrix protein elastin, which, with a half-life of 40 years, is one of the most stable proteins in the body [3]. Despite this stability, fatigue of elastin fibers and lamellae can occur by the sixth decade of life from the accumulated cyclic stress of more than 2 billion expansions of the aorta during ventricular contraction. Long-standing cyclic stress in the media of elastin-containing arteries produces fatigue and eventual fracturing and disarray of elastin along with structural changes of the extracellular matrix that include proliferation of collagen (which is 100–1000 times stiffer than elastin) and deposition of calcium. Humoral factors, cytokines, and oxidative metabolites may also have a role in this process [3]. This process, classically termed *arteriosclerosis*, results in increased stiffness of the aortic wall and ultimately in the development of ISH.

Importantly, not all arteries become stiff with aging. Whereas, long-term structural changes with aging cause increased stiffness of the thoracic aorta and its branches, the more peripheral muscular arteries (such as the brachial and femoral artery) retain their normal viscoelastic properties or may even become less stiff in people with hypertension.

To summarize: in the absence of changes in CO and stroke volume (SV), SBP rises with both increased PVR and increased arterial stiffness; DBP rises with increased PVR and falls with increased arterial stiffness; MAP rises with increased PVR; and PP rises primarily with increased arterial stiffness and to a lesser extent with increased PVR, so that ISH is associated with increased PP — with or without an increase in PVR.

PULSE WAVE MORPHOLOGY AND FUNCTION

The morphology of any pulse wave results from the summation of incident (forward-traveling) and reflected (backward-traveling) pressure waves [3]. Timing depends on both pulse wave velocity (PWV) and distance to the predominant or “effective” reflecting site. Amplitude depends on the amount of impedance mismatch at this effective reflecting site. A marked increase in stiffness or impedance at the reflecting site generates a larger reflected wave.

PULSE WAVE AMPLIFICATION

The intrinsic central-to-peripheral stiffness gradient in the normal vascular tree, along with tapering of the aorta, lead to amplification of the initial or forward pulse wave as it travels distally [3]. Pulse wave amplification causes central aortic PP to be lower than peripheral brachial PP in a healthy young adult. This phenomenon is clinically important in that BPs determined at intermediate sites such as the brachial artery are different from pressures measured simultaneously at the proximal aortic root or in more distal peripheral arteries. Thus, alterations in brachial BP may not fully represent either changes in central BP or pulsatile load in various conditions.

In young adults (late teens, early 20s) with full height and maximum elasticity of their central arteries, PWV is low but impedance mismatch is high. Thus, there is a relatively large reflected wave but it returns to the aorta in mid-late diastole, leading to little or no augmentation of the central pressure, but a maximum boost in coronary blood flow. Between 20 and 50 years of age, aortic PWV increases and now the reflected wave returns in late systole, thereby augmenting central PP in direct proportion to a decrease in the amplification levels. At around 50 to 60 years of age, however, aortic stiffness (carotid to femoral PWV) reaches and then exceeds peripheral arterial stiffness (carotid to brachial PWV) [6]. As a result, reflection at this interface is reduced and reflecting sites shift distally. This “*impedance matching*” at the proximal reflecting sites leads to increased transmission of pulsatility distally with a resulting increased brachial artery PP and the development of ISH, as well as increased pulsatility into the microcirculation [6].

To summarize, age related stiffening is more pronounced in the central arteries of older persons; conversely changes in wave reflection are more marked in younger people. Therefore, the increase in aortic PP and the development of ISH after age 50–60 years is more related to increased arterial stiffness and forward wave projection as measured at the brachial artery. In contrast, the increase in aortic PP and stable brachial PP in those individuals <50 years of age with diastolic-systolic hypertension is due mainly to early wave reflection with increased central augmentation and substantial loss of amplification.

PATHOPHYSIOLOGY OF ISH

By definition, ISH in the elderly is characterized by an increase in PP, frequently but not always by an increase in MAP, and rarely by an increase in stroke volume or ejection rate. Both cross-sectional and longitudinal population studies show that SBP rises from adolescence, whereas DBP, although initially increasing with age, levels off at about age 50 and decreases after age 60 [1, 7]. Thus, PP begins to increase after age 50. The rise in SBP and DBP up to age 50 can best be explained by the dominant effect of PVR (Table 9.1). The transition age of 50–60 years when DBP levels off constitutes a near balancing of increased resistance and increased thoracic aortic stiffness. By contrast, after age 60, the fall in DBP and the rapid widening of PP become surrogate indicators of central elastic arterial stiffening. Indeed, after age 60, central arterial stiffness, rather than PVR, becomes the dominant hemodynamic factor in both normotensive and hypertensive individuals.

The increase in PP may be useful as an adjunct to SBP in predicting CV risk. Indeed, this pattern of ISH with increased PP has been associated with a variety of CV complications [3].

Table 9.1 Hemodynamic patterns of age-related changes in blood pressure

Age(years)	DBP (mmHg)	SBP (mmHg)	MAP (mmHg)	PP (mmHg)	Hemodynamics
30–49	↑	↑	↑	→ or ↓	R>S
50–59	→	↑	→	↑↑	R=S
≥60	↓	↑	→ or ↓	↑↑↑↑	S>R

DBP = diastolic blood pressure; SBP = systolic blood pressure; MAP = mean arterial pressure; PP = pulse pressure; ↑ = increase, ↓ = decrease, → = no change; R = small-vessel resistance, S = large-vessel stiffness (adapted with permission from [7]).

Cardiac complications consist of left ventricular hypertrophy, atrial fibrillation, systolic and diastolic dysfunction, and heart failure (HF). Large artery complications consist of myocardial infarction as well as both hemorrhagic and thrombotic stroke. Microvascular complications consist of cerebral white matter lesions, leading to cognitive impairment, and progressive chronic kidney disease, frequently resulting in ESRD.

In addition to arterial stiffening, the left ventricle itself becomes non-compliant, perhaps as an adaptation to facilitate cardiac ejection and maintain matched coupling of heart to arteries [8]. This is particularly notable in hearts that develop left ventricular hypertrophy, a common occurrence in the elderly, and particularly in those individuals with ISH. Whereas reflected waves normally return during diastole and thereby enhance coronary perfusion, this increased boost is absent in elderly persons with ISH [3]; the decline in DBP, however, rarely falls to the critical level (~50–60 mmHg) required to fall below coronary flow auto-regulation unless, perhaps, there is advanced coronary artery disease [9, 10]. This suggests that the frequent reduction in DBP that accompanies increased PP in patients with ISH may not only be associated with compromised coronary perfusion, but also may be a surrogate marker for increased ventricular-arterial stiffness. Furthermore, *coupling disease*, resulting from stiffness of both the heart and arteries, gives rise to diastolic dysfunction and HF; this results from the combination of an elevated cardiac afterload presented to a compromised left ventricle, which is unable to handle the pressure load [8].

Paradoxically, pressure wave amplification distorts the relationship between central and peripheral PP (and SBP), as measured at the brachial artery by the sphygmomanometer [3]. Therefore, increases in central and not peripheral PP (and SBP), regardless of age, determine increases in cardiac afterload and hence cardiac risk. The changing pattern of age-related brachial artery BP components that predict CV risk results from altered peripheral resistance, aortic stiffness, and wave reflection, all acting in concert to raise SBP, decrease DBP, and diminish pressure amplification; this leads to an age-related shift from sphygmomanometric-determined DBP to SBP and ultimately to ISH with wide PP as more important predictors of CHD risk (Figure 9.1) [11]. These findings represent a significant paradigm shift in our understanding in how we should use brachial artery cuff BP components to predict CV risk.

Previous studies that championed a single BP component as a predictor of CV risk examined a limited spectrum of the overall hypertensive population. When PP, a measurement of stiffness, is combined with MAP, a measurement of resistance, the two major physiologic components of hydraulic load can be effectively related to CV risk [12]; single BP components cannot do this as well [12]. Combining SBP and DBP is equally useful in defining CV risk, but the non-linearity of DBP tends to distort this relationship. However, increased CV risk secondary to increased vascular resistance can be deduced indirectly from concordantly

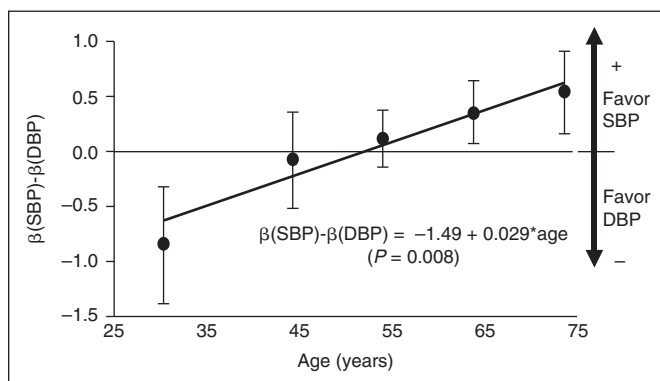


Figure 9.1 Difference in coronary heart disease prediction between systolic blood pressure (SBP) and diastolic (DBP) as function of age. Difference in β coefficients (from Cox proportional-hazards regression) between SBP and DBP is plotted as function of age, obtaining this regression line: $\beta(\text{SBP}) - \beta(\text{DBP}) = -1.49848 + 0.0290 \times \text{age}$ ($P = 0.008$) (with permission from [11]).

high DBP and SBP, whereas increased CV risk secondary to increased arterial stiffness can be deduced indirectly from discordantly high SBP and low DBP (especially DBP values <70 mmHg) that result in a high PP [12].

ETIOLOGY OF ISH

As suggested by their age-dependent divergent patterns of onset, diastolic hypertension (“essential” or primary hypertension) and ISH may be two distinct disorders with significant overlap. The conversion from diastolic-systolic hypertension to ISH in the older age group has been attributed to “burned-out” diastolic hypertension. While some people who have had untreated or poorly-treated diastolic hypertension at a younger age develop ISH as they become older, data from the Framingham Study suggests that only about four out of ten patients acquire ISH in this manner (Figure 9.2) [13]. In contrast, six out of ten people who develop ISH may show a slight rise in DBP over time, but do not go through a stage of diastolic hypertension [13].

This *de novo* form of ISH may have many different causes that include the following:

1. **Type 1 diabetes mellitus:** Ronnback and colleagues [14] found that ISH developed some 15 to 20 years sooner and was three times more frequent in a Finnish group of type 1 normoalbuminuric diabetics as compared with a non-diabetic background population. The premature rise in PP was strongly related to the duration of exposure to hyperglycemia, male sex, and the development of diabetic kidney disease.
2. **Osteoporosis with vascular calcification:** Bone-mineral loss has been associated with ISH both in elderly white women [15] with women in the highest quartile of aortic calcification having a four times higher annual bone loss and a greater propensity for CV disease [16].
3. **Chronic kidney disease (CKD) with vascular calcification:** In a recent study, there was a step-wise increase in the prevalence of ISH as CKD progressed from Stage 3 to 5 [17]. Furthermore, in patients with CKD, aortic vascular calcification occurs earlier and out of proportion to aging.
4. **Intrauterine fetal growth retardation:** Martyn and Greenwald have hypothesized that there is impaired synthesis of elastin during the critical period of fetal development in association

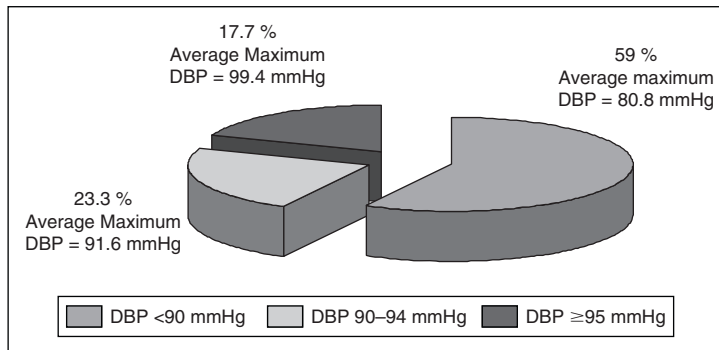


Figure 9.2 Average maximum diastolic blood pressure reached prior to the development of isolated systolic blood pressure for those who reached a diastolic blood pressure of <90 mmHg, from 90 to 94 mmHg, and ≥95 mmHg, respectively (adapted with permission from [13]).

with low birth weights, which results in an accelerated rise in PP [18]. This hypothesis was based on a study of 50-year-old men and women that showed increased aortic pulse wave velocity, a measure of aortic arterial stiffness to be related to size at birth [19].

5. **Repaired coarctation of the aorta:** Patients with successful repair of coarctation of the aorta frequently have residual ISH during rest and after exercise, which has been associated with *coupling disease*, (i.e. increased stiffening of the left ventricle and proximal aorta) and have an increased propensity for CV and cerebrovascular complications [20].
6. **Reduced diameter of the proximal aorta:** Mitchell and colleagues has shown that PP is elevated out of proportion to the increase in MAP in patients with ISH [21]. Elevated *characteristic impedance* and reduced effective diameter of the proximal aorta were major determinants of the rise in PP in both men and women [21].
7. **Advanced aging of the proximal aorta:** McEniery *et al.* have shown that aortic calcification correlated with aortic stiffness, as measured by PWV (after correcting for age and MAP) in patients with ISH who were otherwise healthy and medication-free. Indeed, the magnitude of aortic calcification correlated with the severity of ISH and with the resistance in achieving therapeutic SBP goal levels [22]. This resistance to controlling SBP may be directly the result of using traditional drugs that largely produce vasodilatation rather than decrease arterial stiffness.

In summary, hypertension has largely become a condition affecting older persons, i.e. a minority of those with “burned-out” diastolic ISH and a majority of those with *de novo* ISH of multiple origins that primarily affects proximal aortic stiffness — frequently associated with increased aortic calcification and occasionally with disordered synthesis of elastin.

EPIDEMIOLOGY OF ISH

Approximately 65 million individuals in the United States and 1 billion worldwide are affected by hypertension [23]. The National Health and Nutrition Examination Survey (NHANES III, 1988–91) [2] showed that three out of four adults with hypertension were age 50 years or older. Moreover, about 80% of untreated or inadequately treated individuals with hypertension from age 50 and older had ISH, which by definition represents wide pulse pressure hypertension [2]. Of particular interest is the transition of hypertension subtype with increasing age. From NHANES III data (Figure 9.3), the predominant form of hypertension among those age <50 years is isolated diastolic hypertension (SBP <140 mmHg and DBP >90

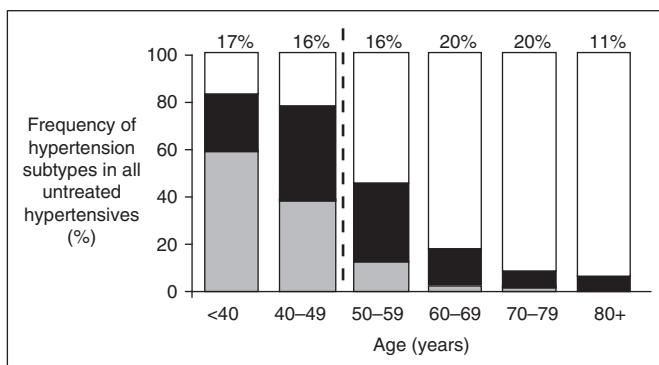


Figure 9.3 Frequency distribution of untreated hypertensive individuals by age and hypertension subtype. Numbers at the tops of bars represent the overall percentage distribution of all subtypes of untreated hypertension in the age group (NHANES III, 1988 to 1994) (with permission from [2]).

- IDH, isolated diastolic hypertension (SBP ≥ 140 mmHg and DBP < 90 mmHg)
- SDH, systolic-diastolic hypertension (SBP ≥ 140 mmHg and DBP ≥ 90 mmHg)
- ISH, isolated systolic hypertension (SBP < 140 mmHg and DBP ≥ 90 mmHg)

mmHg) and systolic-diastolic hypertension (SBP > 140 mmHg and DBP > 90 mmHg), which together account for approximately 80% of persons with hypertension from age 18 to 49 years [2]. Beginning with the decade of 50 to 59 years of age, the predominant form of hypertension is ISH, accounting for more than 55% of those with hypertension aged 50–59, approximately 80% of the hypertension in those aged 60–69, and approximately 90% of those with hypertension aged 70 years or greater. Thus, ISH is the most common subtype of hypertension. Furthermore, a recent analysis of data from the Framingham study showed that normotensive persons reaching age 65 had a 90% lifetime risk of developing hypertension, which was almost exclusively of the ISH subtype, if they lived another 20 to 25 years [24].

MANAGEMENT OF ISH

CLINICAL TRIALS SUPPORTING BENEFITS OF BP REDUCTION

During the past several decades, the treatment approach for elderly patients with hypertension has changed considerably. In the early 1970s, the prevailing wisdom questioned the benefit of antihypertensive agents in patients over age 65 [25]. In 1991, the landmark double blinded, placebo-controlled Systolic Hypertension in the Elderly Program (SHEP) study first established that older patients with ISH benefited from the lowering of SBP with antihypertensive medication [26]. The Systolic Hypertension in Europe (Syst-Eur) [27] and Systolic Hypertension in China (Syst-China) [28] trials thereafter corroborated these findings. Staessen and colleagues conducted a meta-analysis of 11 825 patients who participated in these major trials, as well as an additional 3 868 subjects with ISH, aged 60 years or greater, who participated in five other trials [29]. This analysis found that antihypertensive treatment significantly reduced fatal and non-fatal coronary events by 23% ($P = 0.001$), fatal and non-fatal strokes by 30% ($P < 0.0001$), CV events by 26% ($P < 0.0001$), CV mortality by 18% ($P = 0.01$), and total mortality by 13% ($P = 0.02$) [29]. Additionally, a highly significant 49% reduction in fatal and non-fatal HF was reported using data from the SHEP study ($P < 0.001$) [26]. These results clearly demonstrated that antihypertensive treatment in patients over 60 years of age reduced morbidity and mortality. Furthermore, these studies belied prior

assumptions that age-related changes in BP were somehow “normal” and reinforced the emerging paradigm that treatment will benefit patients with elevated SBP, even when they have normal or reduced DBP.

THE BENEFIT OF TREATING THE VERY OLD

Currently life expectancy in the United States is 77 years [30], raising the question of the benefit of antihypertensive agents in patients this age or older. A meta-analysis of several trials that included 1670 patients of age 80 years or older, suggested even very old patients might benefit from antihypertensive treatment [31]. In those patients, active treatment produced a 34% reduction in stroke ($P = 0.014$), a 39% reduction in HF ($P = 0.01$), and a 22% reduction in major CV events ($P = 0.01$). However, the reduction in coronary events was not statistically significant and there was a non-significant 6% increase in mortality.

The Hypertension in the Very Elderly Trial (HYVET) study [32], a more definitive intervention trial of the very old (from 80 to 105 years of age), utilized a randomized, double-blind, placebo-controlled protocol in 3845 subjects with sustained SBP of 160 mmHg or more, largely with ISH. Active treatment consisted of the diuretic indapamide and when necessary the angiotensin-converting enzyme (ACE) inhibitor perindopril versus matching placebo treatment, to achieve the target BP of <150/80 mmHg. This study, with a significant number of patients with stage 2 ISH showed that there was a significant reduction in both fatal and non-fatal strokes (−4%), HF (−72%), and a reduction in both CV (−27%) and all-cause mortality (−28%) [32]. Therefore, there is now overwhelming evidence that effective pharmacological treatment of both systolic-diastolic hypertension and ISH reduces CV events in the elderly of any age.

The Baltimore Longitudinal Study on aging showed that elevated PP and PWV were related to cognitive impairment, based on decline in verbal and non-verbal memory test scores, in non-demented middle-aged individuals [33]. Furthermore, a recent meta-analysis of three large intervention trials of antihypertensive therapy in elderly hypertensives with ISH (with and without prior strokes) shows that effective lowering of SBP significantly reduced the risk of vascular dementia and Alzheimer syndrome (odds ratio 0.75; 95% CI 0.64–0.94; $P = 0.01$) [34]. Thus, early treatment of high-normal BP to prevent the development of ISH and perhaps aggressive, early treatment of established ISH, by decreasing pathologic aging of cerebral blood vessels, may protect against dementia. However, incident dementia and BP lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG) were inconclusive, perhaps because of the 2.2 year duration of the study, a relatively short timeframe [35]. Clearly, further investigations are needed before we can conclusively prove that effective control of hypertension prevents the developments or slows the progression of dementia.

THERAPEUTIC TARGET GOALS FOR ISH

There are Joint National Committee Seven (JNC-7) [36], European Society of Hypertension and Cardiology [37], and American Heart Association [38] guidelines for the optimal reduction of SBP to achieve maximum benefit from antihypertensive therapy. These guidelines based on observational as well as on outcome data, suggest that low-risk patients be treated to a target goal of SBP <140 mmHg. For high-risk subjects, such as those with diabetes mellitus, CKD, CHD, and stroke, the therapeutic target goal is a SBP <130 mmHg. In addition to reaching target SBP, the paramount goal of therapy in patients with ISH is to achieve the maximum reduction in overall CV risk through simultaneous treatment of all reversible CV risk factors. At the present time, however, there are no outcome studies in the very old to determine what should be the treatment-induced optimal reduction in SBP.

VALUE OF LIFESTYLE INTERVENTION

A variety of lifestyle interventions have been shown to lower SBP in patients with ISH; the most effective of which is successful weight reduction in overweight and obese hypertensives [39]. Even a reduction of 10 to 15 pounds can have a significant benefit in lowering SBP. Older hypertensive patients are usually more salt sensitive than the young, especially in those with ISH [40]. However, any reduction in BP by way of salt restriction depends to a large extent on limiting processed foods with high salt content. The more recent use of the Dietary Approach to Stop Hypertension (DASH) diet [41] (rich in fruits, vegetables, high-calcium but low animal fat foods) has been successful in reducing BP in older hypertensives even when they have an average salt intake. Except for the unusually compliant patient, lifestyle intervention is generally unsuccessful in fully correcting ISH.

SELECTION OF SPECIFIC ANTIHYPERTENSIVE DRUG THERAPY FOR ISH

Unfortunately, conventional antihypertensive drugs in the patient with ISH fall short of optimally reducing age-related increases in PP [42]. The question of which drug class is best suited to start first in patients with ISH remains controversial. Diuretics and calcium channel blockers (CCBs) have been shown to be effective in reducing CV events in major intervention studies [35]. Furthermore, in a substudy of The Losartan Intervention For Endpoint Reduction (LIFE), a trial of patients with ISH and left ventricular hypertrophy, losartan (an angiotensin II receptor blocker [ARB]) was superior to atenolol (a β -blocker) in preventing fatal and non-fatal strokes [43]; importantly, the diuretic hydrochlorothiazide was an add-on drug in more than 70% of both therapeutic arms, suggesting that the combination of a diuretic and ARB is effective in stroke prevention in ISH patients.

More recently, the Avoiding Cardiovascular events through COMbination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial compared morbidity and mortality among 11 400 high-risk men and women (average age 68 years) randomized to 1 of 2 initial combination regimens: a CCB (amlodipine) plus an ACE inhibitor (benazapril) *versus* a diuretic (hydrochlorothiazide) plus an ACE inhibitor (benazapril) [44]. Both regimens reduced BP equally to $<140/80$ mmHg in more than 75% of patients; surprisingly, there was a 20% greater reduction in CV morbidity and mortality endpoints in the ACE inhibitor/CCB arm as compared with the ACE inhibitor/diuretic arm (HR, 0.80 [0.71–0.90]; $P = 0.0002$). Thus, no longer should recommendations routinely favor a diuretic over a CCB, especially when therapy is begun with two antihypertensive agents. In practice, a combination of two or more drug classes will be necessary for BP control in the majority of patients with ISH, especially when SBP is >160 mmHg or when SBP is >140 mmHg in the presence of high risk ISH (the 20/10 rule as per JNC 7) [36].

The optimal strategy in treating ISH is to maximize SBP reduction while minimizing the reduction in DBP. Antihypertensive therapy that decreases vascular resistance will result in a parallel reduction in SBP and DBP in young hypertensives [2]. In contrast, drug-induced reduction in large artery stiffness will result in a greater fall in SBP than in DBP in elderly hypertensives [2]. Therefore, antihypertensive therapy, designed to improve large artery stiffness, will decrease SBP while minimizing the reduction in DBP and in so doing maximize any associated decrease in PP. This occurs in direct proportion to both the age of the patient and the degree of large artery stiffness.

The benefits derived from antihypertensive therapy in the patient with ISH may result from at least five different mechanisms. First, reduction of downstream peripheral resistance will decrease large artery stiffness upstream by a reduction in distending pressure that then decreases the stretch on elastic arteries; a variety of antihypertensive agents, such as CCBs, ACE inhibitors and ARBs that dilate arteries, work in this manner [45]. Second, vasodilatation of small arteries and arterioles will shorten the artery reflection sites, decrease early

wave reflection, diminish aortic late SBP peaking and hence decrease cardiac afterload without a change of the structural basis for arterial stiffness [3, 45]. Nitrates, in doses which do not affect PVR, have been shown to decrease early wave reflection, decrease central PP and hence lower left ventricular afterload — all without a significant change in arterial stiffness [46]. Third, long-term reduction in cardiac afterload will eventually result in regression of left ventricular and smooth muscle hypertrophy, and remodeling of small blood vessels toward a more normal wall to lumen ratio [47]. Indeed, the ability of ACE inhibitors and ARBs to promote regression of left ventricular hypertrophy and arterial remodeling may have important long-term benefits in reducing arterial stiffness [45]. Fourth, therapy which blocks excessive aldosterone at the tissue level may over time result in regression of fibrosis in the heart, renal mesangium, and large blood vessels. In that regard, the aldosterone receptor antagonists spironolactone and eplerenone may prove to be of value in reversing the stiffness of arteries in persons with ISH [48]. Fifth, certain antihypertensive agents appear to possess properties that specifically influence arterial stiffness without affecting peripheral vascular resistance, such as agents that serve as AGE crosslink breakers [49]. Furthermore, a non-crosslink breaker, such as a ligand for the receptor RAGE, leads to changes in the production of extracellular matrix proteins (elastin and collagen) that result in alteration in vascular elasticity [50].

ACHIEVING THERAPEUTIC GOALS

Not unexpectedly, in the management of hypertension 86% of treatment failures occurred in individuals >50 years of age, most of whom had ISH [2]. Using data from the Framingham study, Lloyd-Jones and colleagues demonstrated age-related changes in the ability of subjects to reach target DBP and SBP goals [51]. More patients over the age of 75 than under the age of 60 achieved their DBP goal (92% versus 85%, respectively). In contrast, the SBP target became progressively more difficult to reach: in patients less than age 60, 69% reached their SBP target goal; in those ages 61 to 75 years, 48% of patients reached goal; and in those over the age of 75 years, only 34% reached goal [51].

That the target SBP apparently becomes more difficult to achieve with aging might be explained, in part, by physician inertia. In the past, treatment guidelines focused on the DBP, while largely ignoring control of SBP. Some clinicians feared reaching excessively low DBP and, therefore, accepted SBP above 140 or even 150 mmHg to “protect” DBP. This fear of excessive therapeutic lowering of DBP — the so called “J curve phenomenon” — has been exaggerated. If there is any significant risk of precipitating an ischemic cardiac event with therapy-induced low BP, it would occur only with DBP reduction below 60–70 mmHg, as indicated in a *post hoc* analysis of the SHEP study [12]. Failure to use optimal polypharmacy, and, in particular, failure to incorporate diuretics as part of a multidrug regimen, may have hampered the ability to control ISH. In addition, not treating to the lower target goals in high-risk patients likely further contributed to the disappointingly large percentage of SBP above treatment goal. There is always some risk in reducing BP excessively, particularly in the elderly; however, the available evidence would suggest that adverse events are no more frequent in the elderly than in younger hypertensive subjects. However, it may be appropriate to start with lower doses of medication in the elderly and then titrate slowly against response and symptoms. Although lower initial medication doses may sometimes be indicated to minimize symptoms in elderly hypertensive patients, ultimately most will require and tolerate standard doses and multiple drugs to reach BP targets. However, to prevent overtreatment, BP should be monitored while both sitting and standing and one should inquire as to symptoms of orthostasis; *if orthostasis is present, the standing BP sets the limits for titration of medication.*

To further guard against excessive lowering of BP with polypharmacy, home self-measurement of BP can be an important tool [52]. Self-measurement of BP not only provides informa-

tion for assessing response to antihypertensive medications and improving patient adherence with therapy, but also helps diagnose white-coat effects and masked hypertension; the former requires restraint in medicating and the latter, perhaps, more aggressive therapy than indicated by office BP readings [51]. In addition, self-monitoring of BP is more likely to provide consistency of control and to be cost-effective in avoiding over- or undertreatment.

SUMMARY

Once considered an inconsequential part of the aging process, the development of ISH represents a late manifestation of increased arterial stiffness in the middle-aged and elderly population. Its association with an increased risk for vascular events – such as CHD, stroke, HF, peripheral artery disease, CKD and dementia – highlights the importance of its control. Furthermore, there is overwhelming evidence that pharmacological treatment of both systolic-diastolic hypertension and ISH reduces CV events in the elderly. Treatment benefits of hypertension are greater in the old than in the young, but paradoxically, ISH remains more difficult to control than diastolic hypertension and most middle-age and elderly hypertensive patients fail to achieve recommended targets. In part, the lack of strict control of ISH in the aged population lies in the hemodynamic differences between diastolic and systolic hypertension. Younger patients tend toward isolated diastolic hypertension or combined systolic-diastolic hypertension, primarily driven by increased PVR and are more easily and effectively treated by antihypertensive medications. In contrast, older patients develop ISH in association with increased arterial stiffness, a type of hypertension that is less amenable to current therapies. This barrier to control of ISH may be overcome, largely but not in every case, by an aggressive polypharmacologic approach to therapy.

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Management of hypertension in patients with coronary artery disease

C. Rosendorff

BACKGROUND

Patients with hypertension are at much higher risk of developing all types of occlusive vascular disease, including coronary artery disease (CAD) [1]. Occlusive CAD may limit myocardial perfusion and, therefore, oxygen supply. In hypertension, myocardial oxygen demand is increased for two reasons: first, because of the increased output impedance to left ventricular ejection, and second, because hypertension can cause left ventricular hypertrophy. This combination of decreased oxygen supply and increased oxygen demand explains why hypertensive patients are more likely than normotensive individuals to develop angina pectoris, to have a myocardial infarction (MI) or other major coronary event, and to be at higher risk of dying following MI.

The association of hypertension with arteriosclerotic disease, including CAD, does raise the interesting question of causality. Does the hypertension produce arteriosclerosis, or vice versa? It was thought, during the 1970s and 1980s, that the initial pathophysiologic abnormality in hypertension in young people is an increased cardiac output, the autoregulatory response to which is an increase in peripheral resistance. This physiologic vasoconstriction progresses to structural changes in resistance vessels, which will then perpetuate the hypertension, even though the cardiac output returns to normal. We now know that arteriosclerotic disease is the consequence of a complex interaction of inflammatory cytokines, free radicals, growth factors, lipids, and endocrine and paracrine factors. Many of these adversely affect endothelial function, and have, as a final common pathway, hypertrophy and reduced compliance of large and medium sized arteries and arterioles. These changes are frequently present before the blood pressure (BP) is elevated, and may occur in the offspring of hypertensive parents, supporting the idea that there is a genetic component, but also, and significantly, that the hypertension is a consequence of the vasculopathy. A positive feedback loop then develops, whereby the hypertension makes the arteriosclerosis and its complications worse, by fragmenting elastin fibers, and causing collagen deposition and cross-linking in arteries, contributing to thickening and stiffening of those arteries. Hypertension also induces endothelial dysfunction, reducing endothelium-dependent vasodilator capacity.

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RATIONALE FOR NEW GUIDELINE RECOMMENDATIONS

While there are well-known published guidelines for the management of hypertension, including JNC 7 [2] and equally well-known American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for managing CAD [3–5], there has never previously been an attempt at a systematic review of acceptable treatment options for patients with both conditions. It was the close interaction between hypertension and CAD that prompted the AHA to constitute a writing committee to establish new guidelines for the management of hypertension both for the prevention of CAD, and for the treatment of established CAD. The AHA Scientific Statement [6] was published in 2007 and contains new recommendations for the target BP in individuals either with CAD or at high risk for developing CAD, as well as recommendations for the management of hypertension in patients with established CAD in all its manifestations.

PRIMARY PREVENTION OF CORONARY ARTERY DISEASE IN PATIENTS WITH HYPERTENSION

There is general agreement that we should promote risk-reducing healthy lifestyles, including smoking cessation, lipid, diabetes mellitus and weight management, a suitable exercise regimen, and in some patients at risk, daily aspirin prophylaxis. Non-drug therapy requires time and patience, so is not always implemented with enthusiasm by busy physicians and only rarely has a major impact on patients. This is unfortunate as the potential gains in the health of the population at large are immense. Drug therapy for aggressive lipid-lowering, tight glycemic control in patients with diabetes mellitus and pre-diabetes, weight loss and smoking cessation are particularly important.

ANTIHYPERTENSIVE DRUGS FOR THE PRIMARY PREVENTION OF CORONARY ARTERY DISEASE

In individuals with hypertension, antihypertensive therapy has had a remarkable effect in reducing cardiovascular (CV) events, including stroke, acute MI, and renal failure. The real issue is whether this is a function of BP lowering alone, or whether certain classes of antihypertensive drugs are better than others by virtue of additional actions independent of BP.

Diuretics and β -blockers

Early clinical trials (Medical Research Council [MRC] Working Party [7], Systolic Hypertension in the Elderly Program (SHEP) [8], Swedish Trial in Old Patients (STOP) [9], and MRC-elderly [10]) used diuretics or β -blockers. In general, these studies showed a significant benefit of treatment for reducing stroke morbidity and mortality in all age groups. However, the reduction in CAD risk with treatment was less than half of that for stroke. Many explanations have been advanced for the dissociation between the good stroke outcomes and the mediocre CAD ones, including the potential arrhythmogenic effects of diuretic-induced hypokalemia, the adverse effects of both diuretics and β -blockers on glucose metabolism, and the poorer efficacy of β -blockers in reducing central aortic pressures [11]. More recent meta-analyses have confirmed the poor efficacy of β -blockers in preventing acute coronary syndrome and coronary death [12], and as a class of drugs which increase the risk of new-onset diabetes mellitus [13, 14]. This is probably not a class effect, as newer β -blockers with vasodilating properties (such as carvedilol and nebivolol) have minimal effects on glycemic control. For these reasons, the latest AHA Scientific Statement on hypertension and CAD [6] omitted β -blockers from the list of appropriate drugs for the first-line therapy of uncomplicated hypertension.

Although thiazide diuretics have similar if not worse metabolic effects than β -blockers, their role in the management of hypertension was solidified by ALLHAT [15], which reported

equal efficacy in preventing fatal CHD events or non-fatal MI between chlorthalidone, amlodipine, and lisinopril in over 30 000 patients with hypertension followed for a mean of just under 5 years.

Calcium channel blockers (CCBs)

In the last two decades, there have been several trials of CCBs for the primary prevention of CV complications of hypertension. The CCB trials, Systolic Hypertension in Europe (Syst-Eur) [16], Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) [17], Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS) [18], Nordic Diltiazem (NORDIL) [19], and International Nifedipine GITS Study (INSIGHT) [20] tended to show a significant degree of prevention of stroke, usually compared with placebo or to a diuretic or β -blocker alone or combined. The absolute risk reduction in CAD deaths or non-fatal coronary events was usually less impressive. A meta-analysis, by the Blood Pressure Lowering Treatment (BPLT) Trialists' Collaboration provided strong support for the benefits of angiotensin-converting enzyme (ACE) inhibitors or CCBs over placebo, and for regimens that targeted lower BP goals, but found that when CCBs were compared with diuretics and/or β -blockers, there was a significant lowering of stroke risk, but no difference in CAD and a 33% increase in heart failure (HF) [21]. Angiotensin-converting enzyme inhibitors were better than diuretics and/or β -blockers for HF prevention and better than CCBs for both CAD and HF prevention. Recently, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)-Blood Pressure Lowering Arm (BPLA) trial was terminated early, because the amlodipine-based treatment (with, as needed, perindopril and doxazosin) proved superior to an atenolol-based regimen (with, as needed, bendroflumethiazide and doxazosin) in preventing CAD events in high-risk hypertensive patients [22]. On the basis of the published trials, it can be concluded that CCBs have not been shown to be superior to ACE inhibitors, in the prevention of coronary events.

ACE inhibitors

In animal models of hypertension, ACE inhibitors prevent or reverse myocardial and vascular hypertrophy, and retard atherogenesis [23]. Recently, much attention has focused on trials of ACE inhibitors *vs* placebo in patients, hypertensive or non-hypertensive, who have established CAD or who are at high risk for CAD. Improved outcomes were found in The Heart Outcomes Prevention Evaluation (HOPE) trial [24] for ramipril, and EUROpean trial on Reduction Of cardiac events with Perindopril in stable Artery coronary disease (EUROPA) trial [25], for perindopril, but not in the Prevention of Events with an ACE inhibitor (PEACE) [26] with trandolapril. Overall, the relative risk ratios for the ACE inhibitor-treated group were 0.80 for CAD, 0.84 for HF, 0.79 for major CV events and 0.74 for CV mortality.

Trials of ACE inhibitors *vs* other antihypertensive therapy have also shown some advantage for ACE inhibitors. Two trials, STOP-2 [27] and Appropriate Blood Pressure Control in Diabetes (ABCD) [28], compared ACE inhibitors with CCBs, with highly significant reductions in the ACE inhibitor patients for the relative risk of CAD, HF, and major CV events, but no difference in stroke or CV death.

The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [29] was a huge (over 42 000 subjects) study comparing outcomes in high-risk patients treated with a thiazide-like diuretic (chlorthalidone), ACE inhibitor (lisinopril), α -blocker (doxazosin) or CCB (amlodipine) as first-line therapy for hypertension. The results showed superiority of the diuretic chlorthalidone over lisinopril or doxazosin in preventing stroke, and over lisinopril, doxazosin, or amlodipine in preventing HF. However, there were no significant differences between chlorthalidone, lisinopril or amlodipine in combined fatal CAD or non-fatal MI (the primary outcome of the study), in combined CAD (the primary outcome, coronary revascularization, or hospitalization for angina), or all-cause mortality. The ALLHAT authors concluded, "*thiazide-type diuretics are superior in preventing one or more major forms of CV disease, and . . . should be preferred for first step antihypertensive therapy.*"

The results of ALLHAT are very controversial. Criticisms have included:

1. That the diuretic used in the trial was not superior to the other drugs in preventing the primary outcome.
2. That the “add-on” drugs (primarily a β -blocker) favored chlorthalidone so that the BP was slightly but significantly lower in the diuretic group.
3. That the superiority of chlorthalidone over doxazosin in preventing HF could have been due to a masking effect of the diuretic in patients with HF and peripheral edema.
4. That long-term diuretic therapy increases the risk of developing diabetes mellitus.

Soon after the ALLHAT results were published, the Australian National Blood Pressure 2 (ANBP-2) trial reported the results of a prospective, randomized, open-label study in elderly patients with hypertension, which showed better outcomes with ACE inhibitors than with diuretic agents, despite similar reductions of BP [30].

Angiotensin-receptor blockers (ARBs)

The use of an ARB for the treatment of hypertension in patients with CAD has a solid foundation in animal studies and surrogate endpoint studies in humans. The Losartan Intervention for Endpoint (LIFE) study was the first large (over 9000 patients) study to evaluate the effects of an ARB on cardiovascular outcomes [31]. Losartan was significantly better than atenolol in reducing stroke, but there were no significant differences for CV mortality or MI. In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, there was no significant difference in the primary endpoint (a composite of nine CV events) between a valsartan-based and an amlodipine-based treatment regimen in high-risk patients [32]. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) [33] showed equivalence between telmisartan and ramipril in patients with vascular disease or high-risk diabetes, but the Telmisartan Randomised Assessment Study in ACE-iNtolerant subjects with cardiovascular Disease (TRANSCEND) [34] was disappointing in that there was no significant improvement in the primary outcome (CV death, MI, stroke, or hospitalization for HF) with telmisartan versus placebo in patients with CV disease or diabetes with end-organ damage.

In a meta-analysis, Staessen *et al.* came to a very conservative conclusion, namely that it may not matter which antihypertensive drug is used; the beneficial effects on cardiovascular outcomes is simply a function of the amount of BP reduction [35]. This conclusion does not accord with animal and smaller human studies that suggest that there are cardio- and vasculo-protective effects of ACE inhibitors, and to a lesser extent, CCBs. This is echoed in the AHA Scientific Statement [6] on hypertension and CAD: “*The choice of drugs remains controversial. There is a general consensus that the amount of BP reduction, rather than the choice of antihypertensive drug, is the major determinant of reduction of CV risk; however, there is sufficient evidence in the comparative clinical trials to support the use of an ACE inhibitor (or ARB), CCB, or thiazide diuretic as first-line therapy, supplemented by a second drug if BP control is not achieved by monotherapy. Most patients will require 2 or more drugs to reach goal, and when the BP is >20/10 mmHg above goal, 2 drugs should usually be used from the outset*” (Table 10.1).

HOW FAR SHOULD THE BLOOD PRESSURE BE LOWERED?

Until recently the consensus target for BP was <140/90 mmHg in general and <130/80 mmHg in individuals with diabetes mellitus or chronic kidney disease [2]. There is now some compelling evidence to support lower goals. An analysis of the 274 patients with CAD who completed the intravascular ultrasound substudy of the Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) trial [36] showed that those subjects with a “normal” BP according to the JNC 7 definition (<120/80 mmHg) had a significant decrease of

atheroma volume, “*prehypertensive*” (120 to 139/80 to 89 mmHg) subjects had no significant change; and “*hypertensive*” (140/90 mmHg) subjects had an increase in atheroma volume.

The epidemiologic data also support lower BP goals. At all ages, the relationship between SBP (or DBP) and CAD and stroke mortality is consistent, robust, and continuous, with no apparent lower threshold value. In a meta-analysis of 61 studies that included almost 1 million adults, BP was related to fatal CAD over the BP range of as low as 115/75 up to 185/115 mmHg [37]. Overall, each 20 mmHg increase in SBP doubles the risk of a fatal coronary event. Looked at another way, each decrease in SBP of 20 mmHg (or 10 mmHg in DBP) halves the risk, right down to the lowest levels reported, about 115/75 mmHg. On the basis of these epidemiological data, it can be argued from a public health perspective that many people with BPs previously regarded as normal could benefit from BP reduction if they are at significant risk for future coronary events for other reasons. There is, therefore, a very powerful historical trend for lower BP goals, and the AHA Scientific Statement on this topic has recommended a target of <130/80 mmHg in all patients with CAD, but also in all individuals who are high risk for developing CAD, defined as a Framingham risk score of 10% or greater [6].

Why stop at 130/80 mmHg? On the one hand, it can be argued from pathophysiological principles that even lower SBP values (i.e. <120 mmHg) may be appropriate to reduce myocardial workload. At the same time, there is a concern that excessive lowering of DBP may impair coronary perfusion.

The coronary vascular bed, like most others, is capable of autoregulating its flow in the face of quite large changes in perfusion pressure (Figure 10.1). The relationship between coronary blood flow F , perfusion pressure P , and coronary vascular resistance R , is $F \propto P/R$. In a rigid tube with a fixed resistance, $F \propto P$. The coronary circulation, however, can alter its resistance, such that an decrease in perfusion pressure P causes coronary vasodilatation (decreased R), so that, if ventricular work is kept constant, flow remains relatively constant, down to a level at which the vasodilatation is maximal (the lower limit of coronary vascular autoregulation). Below that limit, any further decline in perfusion pressure will result in a decreased flow. Since nearly all coronary blood flow occurs in diastole, the perfusion pressure referred to here is the mean diastolic BP.

It is theoretically possible that, in hypertensive patients, the diastolic BP could be reduced by therapy to levels below the lower limit of coronary autoregulation, with a consequent reduction in coronary blood flow. Also, the presence of any significant occlusive coronary atherosclerotic disease will shift the lower limit of autoregulation upwards, making patients less tolerant of low diastolic BPs. The problem is that we do not have any data about the exact diastolic BP level at which this occurs in the intact or diseased human coronary circulation.

Further considerations are the effects of exercise and myocardial hypertrophy. The efficiency with which the coronary circulation copes with exercise depends on the coronary flow reserve, defined as the difference between autoregulated and maximally dilated coronary flow at any given perfusion pressure. In Figure 10.1, curve A_1 represents coronary blood flow over a wide range of perfusion pressures, and the perfusion pressure P_1 is at the lower limit of autoregulation. If the coronary vessels are maximally dilated, there is a steep, linear pressure-flow relationship between pressure and flow (Line D_1), and the coronary flow reserve at one arbitrary perfusion pressure is represented by R_1 . If myocardial hypertrophy is present, total coronary flow is greater, with a higher autoregulatory line (Curve A_2), and a rightward shift of the lower limit of autoregulation. However the pressure-flow relation at maximal vasodilatation is less steep (Line D_2), so that the coronary flow reserve (R_2) at any given perfusion pressure is less. Also, the point at which coronary flow reserve is exhausted (Point P_2) in the hypertrophied heart will coincide with a higher perfusion pressure than normal (Point P_1). The clear message is that, in patients with hypertension and left ventricular hypertrophy, the lower limit of autoregulation is set at a higher level of perfusion pressure (and therefore diastolic BP), and that at any level of perfusion pressure, or diastolic BP, the coronary flow reserve will be less than it would be in the normal ventricle. Another

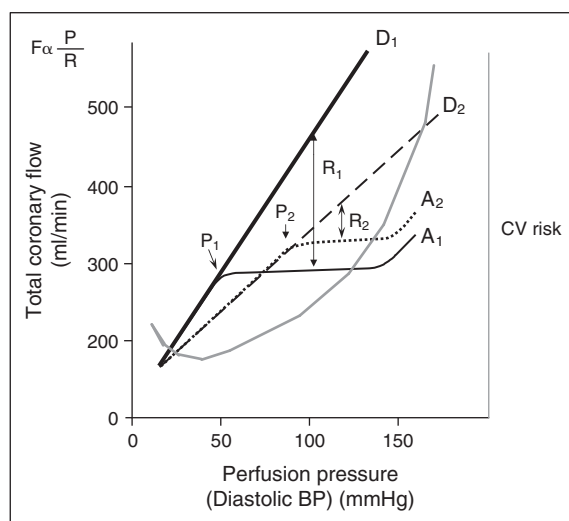


Figure 10.1 Autoregulation of coronary blood flow and myocardial flow reserve in the presence of LV hypertrophy. A_1 represents total coronary blood flow over a range of perfusion pressures (DBP), P_1 is the lower limit of the autoregulatory range, and line D_1 is the pressure-flow relationship in the maximally dilated coronary bed. At any given perfusion pressure, the coronary flow reserve is R_1 . A_2 , P_2 , D_2 and R_2 represent corresponding values in patients with hypertension and/or LV hypertrophy. At any given perfusion pressure, coronary flow reserve is less in the hypertensive/hypertrophied hearts, increasing the vulnerability of the myocardium to ischemia, especially during exercise or any other situation requiring increased coronary flow. Note, also, that the lower limit of coronary autoregulation is shifted to the right (P_1 to P_2) in the hypertensive heart, increasing the vulnerability to a severe drop in perfusion pressure (DBP). The pale continuous line represents a hypothetical 'J-curve', the relationship between diastolic BP and CV risk. The 'up-tick' in CV risk at a diastolic BP of about 40 mmHg is conjectural and not evidence-based.

argument that there is a unique myocardial susceptibility to low diastolic perfusion pressures depends on the understanding that, in contrast to the cerebral circulation, there is maximal oxygen extraction by the myocardium, which therefore cannot compensate for a reduced flow by increasing oxygen extraction.

DOES THIS MATTER? THE J-CURVE

All of this has generated the concept of the "J-curve". Many epidemiologic studies and clinical trials have shown that there is a continuous relationship between diastolic BP and the risk of a coronary event; that is, the lower the diastolic BP, the lower the risk. However a concern is that if diastolic BP is reduced below the lower limit of coronary autoregulation, there will be an up-tick in coronary events, to produce a J-shaped curve. A recent analysis of the Framingham data showed that, in the general population, there is a clearly demonstrable increase in CV risk when the diastolic BP is less than 80 mmHg, but only in those subjects whose systolic BP remains above 140 mmHg [38]. This would make some sense, since the low diastolic BP may reduce coronary perfusion pressure, and the higher systolic BP increases myocardial oxygen demand, and may increase intramyocardial wall tension, thus further limiting perfusion. Another implication is that lowering the systolic BP below 140 mmHg will enable the myocardium to tolerate diastolic pressures below 80 mmHg. These data were obtained in a general population; in patients with occlusive CAD the perfusion pressure downstream of the stenosis would be even further reduced, and the elevated left ventricular

systolic pressure and the presence of left ventricular hypertrophy would further increase myocardial oxygen demand. These considerations are consistent with epidemiologic data that both pulse pressure and presence of left ventricular hypertrophy are strongly predictive of coronary events.

All of this is fine in theory, but seems to have little support from the data of many large clinical trials. In the elderly with isolated systolic hypertension and low DBP, no J-shaped curve has been described with antihypertensive therapy, even though diastolic BP may be reduced even further. In fact the outcome trials in the elderly with isolated systolic hypertension (SHEP [8] and Syst-Eur [16]) together showed decreases of about 25% in myocardial infarction, including sudden death, in the active treatment group compared with those who received placebo. Diabetic patients benefited significantly from aggressive BP lowering in the Hypertension Optimal Treatment (HOT) [39], ABCD [28], and United Kingdom Prospective Diabetes Study (UKPDS) [40] trials, so that current recommendations are to lower BP in diabetic patients to below 130/80 mmHg. A meta-analysis has provided convincing data that the increased mortality of patients with very low DBP (<65 mmHg) reported in some studies was not related to antihypertensive treatment, and was not specific to BP related events [41]. Poor health, including poor left ventricular function, leading to a low diastolic BP and increased risk of death, provides a credible explanation for the J-shaped curve.

There is thus solid epidemiologic evidence, and some clinical trials evidence, that the lower the BP, the better. The AHA Scientific Statement on hypertension and CAD [6] defined the new BP target as <130/80 mmHg in patients with established CAD, but also in individuals with a Framingham risk score of $\geq 10\%$. Nevertheless, because of some lingering doubts about the J-curve, it recommended some caution in lowering the diastolic BP below 65 mmHg, or too quickly, in those patients who have both significant occlusive CAD and an elevated pre-treatment diastolic BP. Fortunately, these are a minority, as these days most hypertensive patients with CAD or with high risk have isolated systolic hypertension.

MANAGEMENT OF HYPERTENSION IN PATIENTS WITH CAD AND STABLE ANGINA

The treatment of patients with symptomatic CAD is directed towards preventing MI and death, and to reducing the symptoms of angina and the occurrence of ischemia. Treatment of risk factors include, besides BP control, smoking cessation, management of diabetes mellitus, exercise training, lipid lowering, and weight reduction in obese patients. There is compelling evidence for the use of antiplatelet agents: aspirin if not contraindicated, otherwise clopidogrel. Other important therapies are short- or long-acting nitrates. The role of revascularization procedures is outside the scope of this review, but it should be noted that, recently, there has been a somewhat reduced enthusiasm for invasive interventions in patients with chronic stable angina as a result of the Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation (COURAGE) trial [42], which showed as good results in preventing coronary events with optimal medical therapy as with percutaneous coronary intervention.

β -BLOCKERS

These reduce the frequency and severity of angina pectoris, improve mortality, and lower BP, and should be the drug of first choice in hypertensive patients with CAD and stable angina. β -blockers reduce cardiac inotropy and slow heart rate and AV conduction. The reduced inotropy and heart rate lower myocardial oxygen demand, while the slowing of the heart rate prolongs the diastolic perfusion time of the coronary arteries, enhancing myocardial blood flow. The reduced cardiac output lowers BP, although there is also a significant BP lowering effect from the blockade of β -adrenoreceptors on the cells of the renal juxtaglomerular apparatus, the major source of circulating renin. Diabetes is not a contraindica-

tion *per se* to the use of β -blockers, although the patient should be aware that most of the symptoms of hypoglycemia may be masked. In stable left ventricular failure, β -blockers (especially carvedilol or metoprolol) may be used as a component of the anti-failure therapy, but should be started at a very low dose and titrated upward very slowly.

When there are contraindications to the use of β -blockers, like obstructive airways disease, severe peripheral vascular disease, or severe bradyarrhythmias such as a high degree of AV block or the sick sinus syndrome, CCBs, either long-acting dihydropyridine agents (like amlodipine, felodipine, or a long-acting formulation of nifedipine), or non-dihydropyridine drugs such as verapamil or diltiazem, are appropriate therapy for angina and hypertension. Calcium channel blockers decrease peripheral resistance, thus reducing BP and LV wall tension, which decreases myocardial oxygen consumption. These drugs also lower coronary resistance, thus enhancing myocardial oxygen supply, especially if there is coronary spasm, as in variant (Prinzmetal's) angina. Non-dihydropyridine CCBs offer the additional benefit of decreasing heart rate.

One study, The Total Ischaemic Burden European Trial (TIBET) [43], has shown equal efficacy of β -blockers and CCBs in controlling stable angina, but most, such as the Angina Prognosis Study in Stockholm (APSIS) [44] and the Total Ischemic Burden Bisoprolol Study (TIBBS) [45], have shown β -blockers to be superior. Long-term outcomes in the International Verapamil Sustained-Release – Trandolapril Study (INVEST) [46] were equivalent, whether the antihypertensive regimen began with verapamil or atenolol. Combining a β -blocker with a dihydropyridine CCB enhances anti-anginal and antihypertensive efficacy. Because of the increased risk of severe bradycardia or heart block if β -blockers are used together with verapamil or diltiazem, long-acting dihydropyridine CCBs are preferred for combination therapy. In the A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system (ACTION) trial [47], the addition of nifedipine GITS to conventional treatment of angina pectoris had no effect on major CV event-free survival, whereas in the CAMELOT study [48], the administration of amlodipine to patients with CAD (most of whom were on a β -blocker) significantly reduced adverse CV events, compared with placebo.

Cardiovascular outcome studies using ACE inhibitors in patients with established CAD but with preserved ventricular function have produced conflicting results. The positive results of the HOPE [24] and EUROPA [25] trials, and the negative results for the PEACE trial [26] have already been referred to. To resolve the discrepancy between HOPE, EUROPA and PEACE, some have pointed to the large differences in how well treated other risk factors were in PEACE, compared with the two other studies. When patients receive all other appropriate therapies (e.g., aspirin, β -blockers, statins), their absolute risk may be so low that the addition of an ACE inhibitor saves very few events, but, nevertheless, on the basis of HOPE and EUROPA, it is entirely reasonable to include an ACE inhibitor in the management of all patients with symptomatic CAD.

MANAGEMENT OF HYPERTENSION IN PATIENTS WITH ACUTE CORONARY SYNDROMES

UNSTABLE ANGINA, NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION, AND ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Patients with *unstable angina* (defined as rest angina, new onset angina, increasing frequency or intensity of previously stable angina, or angina within 6 weeks of a myocardial infarction, but with normal cardiac markers of ischemia) or with *non-ST segment elevation myocardial infarction* (characterized by elevated markers of myocardial injury, such as troponin I or T, or the MB isoenzyme of creatine phosphokinase [CK-MB], but without ST segment elevation) should be admitted to hospital, preferably to a specialized coronary care unit [4, 5]. Anti-ischemic therapy includes bed-rest, continuous ECG monitoring, intravenous nitro-

glycerin, supplemental oxygen, morphine sulfate, and a β -blocker. Cardioselective β -blocker therapy should be initiated intravenously or orally, if the patient is hemodynamically stable. Suitable oral β -blockers are those without intrinsic sympathomimetic activity (such as atenolol, metoprolol, timolol, carvedilol, nebivolol). Carvedilol or metoprolol should be used if there is LV dysfunction (ejection fraction $<40\%$).

Blood pressure should be treated to a goal of less than 130/80 mmHg. The drugs of choice are β -blockers, ACE inhibitors and diuretics. Most patients will require two or more drugs to reach goal, and since all three classes of drugs have also been shown to reduce long-term CV risk in these patients, the use of all three drugs from the outset is not unreasonable.

A number of large, randomized clinical trials, Survival and Ventricular Enlargement (SAVE) study with captopril [49], Acute Infarction Ramipril Efficacy (AIRE) with ramipril [50], and TRACE with trandolapril [51], have shown a significant morbidity and mortality benefit of ACE inhibitors started early in the course of acute MI, complicated by left ventricular dysfunction. In heart failure (Studies of Left Ventricular Dysfunction [SOLVD] [52]), treatment with ACE inhibitors significantly reduced re-infarction, re-admission for heart failure, and mortality; they also improve endothelial function, are antithrombotic and prothrombolytic, and have beneficial effects on ventricular and vascular remodeling.

Two large outcome studies in patients with acute myocardial infarction and left ventricular systolic dysfunction, have compared an ARB to captopril (Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan [OPTIMAAL] [53] and Valsartan in Acute Myocardial Infarction [VALIANT] [54]). In both cases there was no superiority of one drug over the other, and the combination did not further improve outcomes, but tended to increase side-effects. These results confirm the utility of ARBs as alternative therapy in those patients intolerant of an ACE inhibitor because of side-effects, of which a dry cough is the most frequent.

A thiazide diuretic should be added to the pharmacologic regimen if BP control is not achieved with a β -blocker and ACE inhibitor (or ARB), and many would argue, on the basis of the ALLHAT [15] data, that a diuretic should always be prescribed. An aldosterone receptor antagonist may be indicated in patients with an ejection fraction of $\leq 40\%$, or having symptomatic heart failure, provided that the patient does not have significant renal failure or hyperkalemia.

Calcium channel blockers do not reduce mortality rates in the setting of acute MI, and can increase mortality if there is depressed left ventricular function and/or pulmonary edema. If β -blockers are contraindicated, a non-dihydropyridine calcium channel antagonist (e.g. verapamil or diltiazem) can be prescribed for angina control if there is no left ventricular dysfunction. Verapamil or diltiazem should not be added to β -blocker therapy due to the risk of bradycardia or heart block. Second-generation dihydropyridine CCBs, amlodipine and felodipine, have not been studied in acute MI. Nevertheless these agents are frequently used as add-on therapy when β -blockers are contraindicated or inadequate to control angina or supraventricular tachycardia, or as adjunct therapy for BP control.

SUMMARY

In primary and secondary prevention of CAD in patients with arterial hypertension, aggressive BP lowering, to below 130/80 mmHg, is critical, especially in diabetic patients, but care should be exercised in lowering the diastolic BP too low too quickly in patients with significant occlusive CAD whose pre-treatment diastolic BP is high. Although some but not all of the recent trials have shown the superiority of ACE inhibitors over other classes of drugs for the reduction of overall CV morbidity and mortality, the evidence for better CAD outcomes is far from clear. It seems reasonable to recommend the use of a thiazide diuretic, usually with an ACE inhibitor, as first-line drugs in the primary prevention of coronary events in patients with hypertension, with a non-dihydropyridine CCB as an alternative.

Treatment choices for the patient with hypertension and established coronary disease are more straightforward. β -Blockers are effective in the management of hypertension with angina. Long-acting CCBs are an appropriate alternative if β -blockers are contraindicated or not tolerated. If both classes of drug are needed for angina or hypertension control, then a long-acting dihydropyridine CCB should be used with the β -blocker. An ACE inhibitor is also a reasonable option. In acute coronary syndromes, therapy of the hypertension should include β -blockers with an ACE inhibitor (especially if there is LV dysfunction). An ARB may be used as an alternative to ACE inhibitors in all situations. A thiazide diuretic and/or a dihydropyridine CCB could be added for BP control. Verapamil or diltiazem may be used as alternatives to β -blockers in unstable angina, but should not be used together with β -blockers, or if there is depressed LV function or in acute MI.

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Abbreviations

AAMI	Association for the Advancement of Medical Instrumentation
ABCD	Appropriate Blood Pressure Control in Diabetes trial
ABP	ambulatory blood pressure
ABPM	ambulatory blood pressure monitoring
ACC	American College of Cardiology
ACCOMPLISH	The Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension trial
ACE	angiotensin-converting enzyme
ACE-I	angiotensin-converting enzyme inhibitors
ACTION	A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system trial
ADMA	asymmetric dimethylarginine
AGE	advanced glycation end-product
AHA	American Heart Association
AHI	apnea-hypopnea index
AIRE	Acute Infarction Ramipril Efficacy trial
ALLHAT	Antihypertensive and Lipid-Lowering to prevent Heart Attack Trial
AMI	acute myocardial infarction
ANBP	Australian National Blood Pressure study
Ang I	angiotensin I
Ang II	angiotensin II
apoE	apolipoprotein E
APSYS	Angina Prognosis Study in Stockholm
ARB	angiotensin-receptor blocker
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ASH	American Society of Hypertension
AT ₁	angiotensin II receptor type 1
AT ₂	angiotensin II receptor type 2
AV	atrioventricular
BEST	Beta-blocker Evaluation in Stroke Trial
BH4	tetrahydrobiopterin
BHF	British Heart Foundation
BHS	British Hypertension Society
BMI	body mass index
BP	blood pressure
BPLA	Blood Pressure Lowering Arm trial of the Anglo-Scandinavian Cardiac Outcomes Trial

BPLT	Blood Pressure Lowering Treatment trialists' collaboration
CAD	coronary artery disease
CAMELOT	Comparison of Amlodipine <i>vs</i> Enalapril to Limit Occurrences of Thrombosis trial
CANPAP	Canadian Positive Airway Pressure Trial for Patients With Congestive Heart Failure and Central Sleep Apnea
CARATS	Coronary Artery Reactivity After Treatment with Simvastatin study
CCBs	calcium channel blockers
CCS	Chinese Cardiac Study
cGMP	cyclic guanosine-5'- monophosphate
CHARM	Candesartan in Heart Failure Assessment in Reduction of Mortality
CHD	coronary heart disease
CHHIPS	Controlling Hypertension and Hypotension Immediately Post-Stroke trial
CI	confidence interval
CKD	chronic kidney disease
CO	cardiac output
CONSENSUS	Cooperative North Scandinavian Enalapril Survival Study
COSSACS	Continue or Stop post-Stroke Antihypertensives Collaborative Study
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation trial
CPAP	continuous positive airway pressure
CRP	C-reactive peptide
CSA	central sleep apnea
CT	computed tomography
CV	cardiovascular
DASH	Dietary Approach to Stop Hypertension trial
DBP	diastolic blood pressure
DETAIL	Diabetics Exposed to Telmisartan and Enalapril trial
DIABHYCAR	DIABetes Hypertension microalbuminuria or proteinuria Cardiovascular events And Ramipril trial
ECG	electrocardiogram
EDHF	endothelium-derived hyperpolarizing factor
EEG	electrocephalogram
EF	ejection fraction
eGFR	estimated glomerular filtration rate
EMG	electromyograms
ENOS	Efficacy of Nitric Oxide in Stroke trial
eNOS	endothelial nitric oxide synthase
ESH	European Society of Hypertension
ESRD	end-stage renal disease
EUROPA	EUropean Reduction Of cardiac events with Perindopril in stable coronary Artery disease study
EWPHF	European Working Party on Hypertension in the Elderly
FAD	flavin adenine dinucleotide
FDA	Food and Drug Administration
FMN	flavin mononucleotide
GFR	glomerular filtration rate

GISSI-3	Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto miocardico trial
GITS	gastrointestinal-therapeutic-system
HCTZ	hydrochlorothiazide
HDFP	Hypertension detection and follow-up program
HDL	high-density lipoprotein
HF	heart failure
HIF-1 alpha	hypoxia-inducible factor-1 alpha
HOPE	Heart Outcomes Prevention Evaluation
HOT	Hypertension Optimal Treatment trial
HSCSG	Hypertension-Stroke Cooperative Study Group
HYVET	HYpertension in the Very Elderly Trial study
HYVET-COG	HYpertension in the Very Elderly Trial cognitive function assessment
ICAM-1	intercellular adhesion molecule-1
IDH	isolated diastolic hypertension
IDNT	Irbesartan Diabetic Nephropathy Trial
IL-6	interleukin-6
INDANA	Individual Data Analysis of Antihypertensive Intervention trials
INSIGHT	International Nifedipine GITS Study
INTERACT	INTensive blood pressure Reduction in Acute Cerebral hemorrhage Trial
INVEST	International Verapamil Sustained-Release – Trandolapril Study
IRMA-2	IRbesartan MicroAlbuminuria trial
ISH	isolated systolic hypertension
ISIS	International Study of Infarct Survival
JHS	Japanese Hypertension Society
JMS-1	Japan Morning Surge-1 study
JMS-ABPM	Jichi Medical School ambulatory blood pressure monitoring Study
JNC 7	Seventh report of the Joint National Committee on Prevention Detection Evaluation and Treatment of High Blood Pressure
LCD	liquid crystal display
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LIFE	Losartan Intervention For Endpoint reduction in hypertension trial
LLT	lipid-lowering therapy
L-NAME	N(G)-nitro-L-arginine methyl -ester
L-NMMA	N(G) monomethyl-L-arginine
LP-PLA ₂	lipoprotein-associated phospholipid
LV	left ventricular
LVH	left ventricular hypertrophy
MAP	mean arterial pressure
MCP	monocyte chemotactic protein
ME-difference	morning-evening difference
MI	myocardial infarction
MICRO-HOPE	Microalbuminuria Cardiovascular and Renal Outcomes substudy of the Heart Outcomes Prevention Evaluation study
MIDAS	Multicenter Isradipine Diuretic Atherosclerosis Study
MMP-9	matrix metalloproteinase-9
MOSES	MORbidity and mortality after Stroke Eprosartan compared with nitrendipine for Secondary prevention trial
MRC	Medical Research Council

MRI	magnetic resonance imaging
NADPH	nicotinamide-adenine dinucleotide phosphate
NF-kappaB	nuclear factor kappa B
NHANES III	National Health and Nutrition Examination Survey
NIDDM	Non-insulin dependent diabetes mellitus
NIH	National Institutes of Health
NMA	N-methylarginine
NO	nitric oxide
NORDIL	Nordic Diltiazem
NSTEMI	non-ST-evaluation myocardial infarction
NYHA	New York Heart Association
ONTARGET	ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial
OPTIMAAL	Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan
OR	odds ratio
OSA	obstructive sleep apnea
PAI-1	plasminogen activator inhibitor-1
PAMELA	Pressioni Arteriose Monitorate e Loro Associazioni study
PATS	Post-stroke Antihypertensive Treatment Study
PEACE	Prevention of Events with Angiotensin Converting-Enzyme inhibition study
PECAM-1	platelet endothelial cell adhesion molecule (PECAM)-1
PP	pulse pressure
PRA	plasma renin activity
PREVENT	Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial
PRoFESS	Prevention Regimen For Effectively avoiding Second Strokes trials
PROGRESS	Perindopril pROtection aGainst REcurrent Stroke Study trial
PVR	peripheral vascular resistance
PWV	pulse wave velocity
QUIET	Quinapril Ischemic Event Trial
RAAS	renin-angiotensin-aldosterone system
RAGE	receptors for advanced glycation end-products
RAS	renin-angiotensin system
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan
ROS	reactive oxygen species
SAVE	Survival And Ventricular Enlargement trial
SBP	systolic blood pressure
SBPM	Self-blood pressure monitoring
SCOPE	Study on COgnition and Prognosis in the Elderly
SDH	systolic-diastolic hypertension
SHEP	Systolic Hypertension in the Elderly Program
SMC	smooth muscle cell
SMILE	Survival of Myocardial Infarction Long-Term Evaluation trial
SNS	sympathetic nervous system
SOLVD	Studies Of Left Ventricular Dysfunction
STEMI	ST-evaluation myocardial infarction
STOP	Swedish Trial in Old Patients
SV	stroke volume
Syst-China	Systolic Hypertension in China trial

Syst-Eur	Systolic Hypertension in Europe trial
TEST	(atenolol) Evaluation in Stroke Trial
THOP	Treatment of Hypertension Based on Home or Office Blood Pressure trial
TIA	transient ischemic attack
TIBBS	Total Ischemic Burden Bisoprolol Study
TIBET	Total Ischaemic Burden European Trial
TNF	tumor necrosis factor
tPA	tissue plasminogen activator
TRACE	Trandolapril Cardiac Evaluation trial
TRANSCEND	Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease
TREND	Trial on Reversing Endothelial Dysfunction
UA	unstable angina
UAR	urinary albumin excretion ratio
UKPDS	United Kingdom Prospective Diabetes Study
VALIANT	Valsartan in Acute Myocardial Infarction trial
VALUE	Valsartan Antihypertensive Long-term Use Evaluation trial
VCAM-1	vascular cell adhesion molecule-1
VEGF	vascular endothelial growth factor
XO	xanthine oxidase

Index

- ABCD (Appropriate Blood Pressure Control in Diabetes) 117
- ACCOMPLISH (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Isolated Systolic Hypertension) trial 33, 59–60, 66, 68, 109
- 'ACE crash' 79
- acetylcholine, vascular response 12
- ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system) 123
- activated oxygen species, production in eNOS uncoupling 4
- acute coronary syndromes, management of hypertension 123–4
- acute myocardial infarction 124
 - trials of ACE inhibitors 67, 70–2
 - combination with ARBs 72
 - trials in early AMI 71
- acute stroke
 - hypertension 89
 - treatment options 90–1, 97
 - hypotension 90, 95–6
 - optimal blood pressure 94–5
 - treatment to raise blood pressure 91–2
- adhesion molecules 6
- ADMA (asymmetric dimethylarginine) 4
 - in assessment of endothelial function 13
- advanced glycation end-products (AGEs) 9
- AGE crosslink breakers 110
- AIRE (Acute Infarction Ramipril Efficacy) trial 67, 68, 70, 73, 124
- albuminuria reduction
 - ARBs, relationship to dose 58
 - comparison of ACE inhibitors and ARBs 83
- aldosterone
 - plasma concentration, effects of ACE inhibitors and ARBs 82
 - relationship to OSA and resistant hypertension 20
- aldosterone receptor antagonists
 - in acute myocardial infarction 124
 - in isolated systolic hypertension 110
- ALLHAT (Antihypertensive and Lipid-Lowering to prevent Heart Attack Trial) 57, 116–17, 119
- allopurinol, effect on xanthine oxidase activity 12
- alpha, beta-blockers
 - effect on endothelial function 10
 - reduction of morning BP surges 33
- alpha-blockers, reduction of morning BP surges 32, 33
- ambulatory blood pressure monitoring 46–7, 48, 53
 - PAMELA study 42
- ambulatory blood pressure reactivity index 27
- American Heart Association (AHA), Scientific Statement on hypertension and CAD 116, 118, 119
- amlodipine, in control of morning BP surges 32–3
- ANBP-2 (Australian National Blood Pressure 2) trial 119
- angioedema, ACEI-associated 80, 86
- angiotensin II 6, 8
 - plasma concentration, effects of ACE inhibitors and ARBs 82
- angiotensin II type-1 (AT₁) receptor 6
 - overexpression in dyslipidemia 7, 8
- angiotensin II type-2 (AT₂) receptor 82
- angiotensin-converting enzyme inhibitors (ACEIs) 63, 66
 - in acute coronary syndromes 124
 - benefit beyond BP lowering 51–2, 55–7
 - dose-dependence 57–8
 - primary prevention of CAD 117, 119
 - renal protection 73, 82–4
 - secondary stroke prevention 92, 93, 95, 96

- angiotensin-converting enzyme inhibitors (ACEIs) (continued)
 - benefits in high-risk patients 53–5
 - BP lowering effect 74
 - chemical structures 73
 - class effect in CV protection 73–4
 - clinical trials 65–7, 68–9
 - in acute myocardial infarction 67, 70–3
 - comparison with ARBs 86
 - blood pressure reduction 81–2
 - cardioprotection 84–6
 - in high risk CAD patients 58–9
 - renoprotection 82–4
 - side-effects 86
 - comparison of dosing and pharmacologic properties 67
 - early use 79–80
 - effect on morning BP surges 34
 - effects on endothelial function 11
 - humoral responses 82
 - in hypertensive patients with CAD 123
 - in isolated systolic hypertension 109–10
 - mechanisms of action 63–4
 - side-effects 80, 86
 - site of action 65, 81
- angiotensin-receptor blockers (ARBs)
 - in acute myocardial infarction 72, 124
 - albuminuria/proteinuria reduction, relationship to dose 58
 - benefit beyond BP lowering 52
 - primary prevention of CAD 119
 - secondary stroke prevention 93, 95, 96
 - comparison with ACE inhibitors 86
 - blood pressure reduction 81–2
 - cardioprotection 84–6
 - in high risk CAD patients 58–9
 - renoprotection 82–4
 - side-effects 86
 - effect on endothelial dysfunction 11
 - effect on morning BP surges 34
 - humoral responses 82
 - in isolated systolic hypertension 109–10
 - site of action 81
- anti-oxidant effects
 - ARBs 11
 - calcium-channel blockers 10–11
- anti-oxidant vitamins, effect on endothelial function 11–12
- aortic calcification, association with isolated systolic hypertension 106
- apnea–hypopnea index (AHI) 17
- APSYS (Angina Prognosis Study in Stockholm) 123
- arterial stiffness 102, 103
 - reduction 109–10
- arteriolosclerosis 102
- ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) 13, 117
 - Conduit Artery Function Evaluation substudy 53
- Association for the Advancement of Medical Instrumentation (AAMI) validation process 44
- atheroma volume, relationship to blood pressure 119–20
- atherosclerosis
 - association with eNOS deficiency 4–5
 - association with hypercholesterolemia 7
 - association with hypertension 8
- auscultatory gap 40
- automated blood pressure measurement
 - ambulatory monitoring 46–7
 - office readings 41
 - self-BP devices
 - types of monitors 45
 - validation 43–5
 - values for upper limit of normal BP 47
- Baltimore Longitudinal Study 108
- barrier function, endothelium 2
- bedtime-dosing, in treatment of morning BP surges 35
- benazepril
 - ACCOMPLISH trial 59–60, 66, 68, 109
 - dosing and pharmacologic properties 67
- benefit beyond BP lowering 51, 59–60
 - ACE inhibitors 55–7
 - dose dependence 57–8
 - evidence from clinical trials 51–3
 - high-risk CAD patients, comparison of ACE inhibitors and ARBs 58–9
 - see also* cardioprotection; renoprotection
- BEST (Beta-blocker Evaluation in Stroke Trial) 93
- beta-blockers
 - in acute coronary syndromes 124
 - in hypertensive patients with CAD 122–3
 - in primary CAD prevention 116
 - in secondary stroke prevention 93, 95, 96
- BH4 (tetrahydrobiopterin) 2, 4, 6
 - effect on endothelial function 12
- blood pressure load, predictive value 47

- blood pressure measurement
 - algorithm for use of SBPM and ABPM 43
 - automated devices 41
 - correct technique 40
 - cuff size 40
 - features of different methods 46
 - terminal digit preference 39–40
 - 'white-coat' effect 39
 - see also* ambulatory blood pressure monitoring; self-blood pressure monitoring
- brachial artery, pulse wave amplification 103
- brachial artery imaging, assessment of
 - endothelial function 12–13
- bradykinin activity, effect of ACE inhibitors 64, 81–2, 85
- British Hypertension Society (BHS),
 - validation of automated BP devices 44
- calcium channel blockers
 - in acute myocardial infarction 124
 - effect on endothelial function 10–11
 - in hypertensive patients with CAD 123
 - in isolated systolic hypertension 109
 - in primary prevention of CAD 117
 - in secondary stroke prevention 93, 95
- CAMELOT (Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis) trial 119–20, 123
- candesartan
 - after acute ischemic stroke 90–1
 - effect on morning BP surges 34
- CANPAP (Canadian Positive Airway Pressure Trial for Patients with Congestive Heart Failure and Central Sleep Apnea) 23
- captopril
 - in acute MI
 - CCS-1 68, 71
 - ISIS-4 69, 70, 71
 - SAVE trial 67, 68, 70
 - VALIANT 69, 72, 124
 - dosing and pharmacologic properties 67
 - early use 79–80
 - renal protection 66
- CARATS (Coronary Artery Reactivity After Treatment with Simvastatin) study 10
- cardiac dysfunction, risk factors, obstructive sleep apnea 19
- cardioprotection 116–19
 - ACE inhibitors 51–2, 55–7, 64, 66
 - class effect 73–4
 - relationship to dose 57
 - comparison of ACE inhibitors and ARBs 84–6
- cardiovascular disease risk, effect of OSA treatment 22
- cardiovascular risk factors
 - early morning BP surges 28–9
 - effect on endothelial function 6–7
 - diabetes mellitus 8–9
 - dyslipidemia 7
 - hypertension 7–8
 - smoking 9
- carotid atherosclerosis, association with morning BP surges 31
- carvedilol
 - effect on endothelial function 10
 - in treatment of morning BP surges 33
- CCS-1 (Chinese Cardiac Study) 68, 71
- CD40 6
- CD47 6
- CD99 6
- central sleep apnea (CSA) 22–4
- CHARM (Candesartan in Heart Failure Assessment in Reduction of Mortality) trials 80
- Cheyne–Stokes respiration 22
- CHHIPS (Controlling Hypertension and Hypotension Immediately Post Stroke) trial 91
- Chinese Cardiac Study (CCS-1) 71
- chronic kidney disease
 - association with isolated systolic hypertension 105
 - non-dipping nocturnal BP 31
- chronopharmacologically administered medication, in treatment of morning BP surges 33, 34–5
- circadian variability of blood pressure 27, 34, 46
- class effect, ACE inhibitors 73–4
- coarctation of the aorta, repaired, association with isolated systolic hypertension 106
- cognitive impairment, relationship to isolated systolic hypertension 108
- cold pressor testing, effect of olmesartan 11
- Collaborative study of Angiotensin-Converting Enzyme Inhibition and Diabetic Nephropathy 80
- community BP screening 45
- congestive heart failure, central sleep apnea 22–4

- CONSENSUS II (Cooperative North Scandinavian Enalapril Survival Study) 68, 70, 71–2, 74, 80
 continuous positive airway pressure (CPAP)
 in central sleep apnea 23
 in obstructive sleep apnea 21, 22
 coronary artery disease (CAD)
 management of hypertension 122–3, 124–5
 AHA scientific statement 116, 118, 119
 patients with acute coronary syndromes 123–4
 primary prevention 116
 ACE inhibitors 117, 119
 ARBs 119
 calcium channel blockers 117
 diuretics and beta-blockers 116–17
 protective effects of ACE inhibitors and ARBs 85
 relationship to hypertension 115
 see also acute myocardial infarction
 coronary artery disease (CAD) risk, relationship to blood pressure 120
 coronary perfusion 120–1
 COSSACS (Continue or Stop post-Stroke Antihypertensives Collaborating Study) 91
 cough, ACEI-associated 80, 86
 coupling disease, ISH 104, 106
 COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation) trial 122
 cuff size, blood pressure measurement 40
 Cushing reflex 89
 cyclo-oxygenase 5

 DASH (Dietary Approach to Stop Hypertension) diet 109
 dementia, post-stroke, risk factors 97
 dementia risk, effect of treating ISH 108
 DETAIL (Diabetics Exposed to Telmisartan and Enalapril) study 83–4
 diabetes mellitus
 endothelial dysfunction 8–9
 renoprotection, comparison of ACE inhibitors and ARBs 83–4
 type 1, isolated systolic hypertension 105
 use of beta-blockers 122–3
 diabetes risk, diuretics and beta-blockers 116–17
 DIABHYCAR (DIABetes Hypertension, microalbuminuria or proteinuria, Cardiovascular events and Renal Outcomes) trial 57, 58
 diastolic blood pressure
 age-related changes 104
 coronary heart disease prediction 105
 excessive lowering 110, 120–1
 J-curve 121–2
 diastolic hypertension
 epidemiology 107
 progression to isolated systolic hypertension 105, 106
 dietary intervention, value in isolated systolic hypertension 109
 digit bias, blood pressure measurement 39–40
 dipping, nocturnal blood pressure 46
 diuretics
 in acute coronary syndromes 124
 in primary CAD prevention 116–17, 119
 reduction of nocturnal BP 33
 in secondary stroke prevention 93, 95, 96
 diurnal variation 27, 46
 RAS activity 34
 doxazosin, in treatment of morning BP surges 33
 Dublin Outcome Study 29
 dyslipidemia, effect on endothelial function 7

 early AMI, ACE inhibitor trials 71
 elastin 102
 impaired fetal synthesis 105–6
 elderly people, benefits of treating ISH 108
 enalapril 80
 in acute MI, CONSENSUS II 68, 70, 71–2, 74
 dosing and pharmacologic properties 67
 effect on endothelial function 11
 SOLVD trial 67, 68, 70
 endothelial dysfunction 3–4, 115
 adhesion molecules 6
 angiotensin II 6
 eNOS deficiency 4–5
 inflammation 5
 prothrombotic effects 6
 reactive oxygen species production 5
 role in morning BP surges 32
 endothelial function 1–2
 assessment 12–13
 effect of allopurinol 12
 effect of anti-oxidant vitamins 11–12

- effect of antihypertensive medications 10–11
- effect of BH4 12
- effect of cardiovascular risk factors 6–7
 - diabetes mellitus 8–9
 - dyslipidemia 7
 - hypertension 7–8
 - smoking 9
- effect of glitazones 12
- effect of HDL 12
- effect of statins 9–10
- role of nitric oxide 2–3
- endothelial nitric oxide synthase (eNOS) 2, 3
 - deficiency 4–5, 8
 - endogenous inhibitors 4
 - uncoupling 4
- endothelial repair
 - endothelial progenitor cells 9
 - local mitogenesis 9
- endothelin-1 3
 - effect of reactive oxygen species 5
- endothelium-dependent vasodilation 3
- endothelium-derived hyperpolarizing factor (EDHF) 3
- ENOS (Efficacy of Nitric Oxide in Stroke) trial 91
- eprosartan, evidence for benefit beyond BP reduction 52
- EUROPA (EUROpean Reduction Of cardiac events with Perindopril in stable coronary Artery disease) study 54, 59, 67, 68, 70, 117, 123
- European Society of Hypertension (ESH), validation of automated BP devices 44
- fatty streak formation 7
- finger BP devices 45
- foam cells 7
- fosinopril, dosing and pharmacologic properties 67
- gap junctions 1
- GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto miocardico)-3 69, 70, 71
- glitazones, effect on endothelial function 12
- glucose metabolism, effect of diuretics and beta-blockers 116–17
- glutathione reductase 5
- heart failure
 - central sleep apnea 22–4
- effect of enalapril (SOLVD trial) 67
- hidden hypertension 42
- high-density lipoprotein (HDL), effect on endothelial function 12
- high-risk patients
 - benefits of ACE inhibitors 53–5
 - comparison of ACE inhibitors and ARBs 58–9
 - definition 53
- home blood pressure readings 46, 110–11
 - definitions of normal versus hypertensive measurements 45
 - limitations 42–3
 - in monitoring antihypertensive therapy 42
 - number of readings 45
 - prognostic value 41–2
 - transtelephonic monitoring 45–6
 - types of device 45
 - validation of automated devices 43–5
- HOPE (Heart Outcomes Prevention Evaluation) trial 54, 55, 59, 66, 68, 70, 73, 80, 94, 117, 123
- evidence for benefit beyond BP reduction 51–2
- MICO-HOPE substudy 57–8
- HOT (Hypertension Optimal Treatment) trial 53, 122
- hydrogen peroxide, production in eNOS uncoupling 4
- hyperaldosteronism, relationship to OSA and resistant hypertension 20
- hypercholesterolemia
 - AT₁ receptor expression 8
 - effect on endothelial function 7
- hyperkalemia, in ACEI and ARB therapy 86
- hypotension, in acute stroke 90, 95–6
- hypoxia-inducible factor (HIF)-1 alpha 2
- HYVET (HYpertension in the Very Elderly Trial) 108
- IDNT (Irbesartan Diabetic Nephropathy Trial) 52, 80
- impedance matching 103
- INDANA (Individual Data Analysis of Antihypertensive Intervention Trials) 92
- inflammation, in endothelial dysfunction 5
- inflammatory markers, association with morning BOP surges 31
- INSIGHT (International Nifedipine GITS Study) 117
- insulin, effects on endothelium 8

- insulin resistance, endothelial dysfunction 8–9
- INTERACT (INTensive blood pressure Reduction in Acute Cerebral hemorrhage Trial) 91
- interleukin (IL)-6 5
- interleukin (IL)-18 5
- International Protocol, automated BP devices 44
- intracellular adhesion molecule-1 (ICAM-1) 6
- intracranial hemorrhage, blood pressure reduction 91
- intrauterine growth retardation, association with isolated systolic hypertension 105–6
- INVEST (International Verapamil Sustained-Release-Trandolapril Study) 123
- irbesartan
 - IDNT (Irbesartan Diabetic Nephropathy Trial) 52, 80
 - IRMA-2 (second IRbesartan MicroAlbuminuria) trial 58
- ISIS (International Study of Infarct Survival)-4 69, 70, 71
- isolated systolic hypertension (ISH) 101, 111
 - diastolic blood pressure 122
 - epidemiology 106–7
 - etiology 105–6
 - hemodynamics 101–3
 - management
 - achievement of therapeutic goals 110–11
 - benefit of treating the very old 108
 - choice of antihypertensive drug 109–10
 - lifestyle intervention 109
 - therapeutic goals 108
 - trials supporting BP reduction 107–8
 - pathophysiology 103–5
- J-curve 110, 121–2
- Japan Morning Surge-1 (JMS-1) study 33
- Jichi Medical School ambulatory blood pressure monitoring (JMS-ABPM) study 28, 30
- junction adhesion molecules 6
- kidney transplantation, comparison of ACE inhibitors and ARBs 84, 86
- L-arginine-nitric oxide pathway 3
- left ventricle, effect of isolated systolic hypertension 104
- left ventricular hypertrophy, association with morning BP surges 31
- leukocytes, effect of NO 3
- LIFE (Losartan Intervention For Endpoint reduction in hypertension) trial 52, 80, 119
 - ISH substudy 109
- lifestyle intervention, in isolated systolic hypertension 109
- lipoprotein-associated phospholipid (LP-PLA₂) 5
- lisinopril
 - dosing and pharmacologic properties 67
 - in early AMI (GISSI-3) 69, 70, 71
- long-acting drugs, in control of morning BP surges 32–3
- losartan
 - in acute MI (OPTIMAAL) 124
 - anti-oxidant properties 11
 - in isolated systolic hypertension 109
 - non-blood pressure-lowering effects (LIFE) 52, 80, 119
- macrophage, lipid uptake 7
- matrix metalloproteinase 9 (MMP-9) levels, relationship to morning BP surges 31
- mean arterial pressure (MAP) 101–2
 - age-related changes 104
- meta-regression, evidence for ACEI benefit beyond BP reduction 55–7
- MICRO-HOPE (Microalbuminuria, Cardiovascular and renal Outcomes substudy of HOPE trial) 57–8
- microalbuminuria, association with morning BP surges 31
- MIDAS (Multicenter Isradipine Diuretic Atherosclerosis Study) 117
- moexipril, dosing and pharmacologic properties 67
- morning BP surges 27–8
 - association with carotid atherosclerosis 31
 - association with left ventricular hypertrophy 31
 - association with microalbuminuria 31
 - association with silent cerebral infarcts 30
 - association with small artery disease 32
 - cardiovascular risk 28–9
 - and endothelial dysfunction 32
 - management 35–6
 - mechanisms 29–30
 - treatment 32
 - chronopharmacologically administered medication 34–5

- longer-acting drugs 32–3
- RAS inhibitors 34, 35–6
- sympathetic inhibitors 33
- MOSES (MOrbidity and mortality after Stroke, Eprosartan compared with nitrendipine for Secondary prevention) trial 52, 92–3
- nephroprotection *see* renoprotection
- nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase 5
- nifedipine, gastrointestinal-therapeutic-system (GITS) formulation, effect on morning BP surges 35
- nimodipine, in acute stroke 90
- nitrates, in isolated systolic hypertension 110
- nitric oxide (NO) 2–3
 - insulin-induced production 8
- nocturnal BP 46
 - effect of diuretics 33
- nocturnal non-dipping BP
 - in chronic kidney disease 31
 - in OSA-related hypertension 20
- non-BP benefits of therapy *see* benefit beyond BP lowering
- non-ST-segment elevation myocardial infarction, management of hypertension 123–4
- nonenzymatic protein glycation 9
- NORDIL (Nordic Diltiazem) trial 117
- obstructive hypopneas 17
- obstructive sleep apnea (OSA) 17–18
 - clinical presentation 18
 - diagnosis 18–19
 - hypertension 19–20
 - mechanisms 19
 - non-dipping nocturnal BP 20
 - relationship to sleep duration 20–1
 - prevalence 18
 - signs, symptoms and risk factors 18
 - treatment 22
 - continuous positive airway pressure 21
 - effect of antihypertensives 21
- office blood pressure measurement 39–41, 46, 47, 53
- Ohasama study 29, 42
- olmesartan, anti-oxidant properties 11
- ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) 58–9, 69, 72, 81, 86, 119
 - cardiovascular protection 86
 - renal outcomes 84
- OPTIMAAL (Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan) 124
- oscillometric devices, validation 43–5
- osteoporosis, association with isolated systolic hypertension 105
- out-of-office blood pressure monitoring 41
 - see also* ambulatory blood pressure monitoring; self-blood pressure monitoring
- P-selectin 6
 - in prediction of myocardial infarction 13
- PAMELA (Pressioni Arteriose Monitorate e Loro Associazioni) study 42
- paroxysmal nocturnal dyspnea 22
- PEACE (Prevention of Events with Angiotensin Converting Enzyme inhibition) study 54–5, 72, 117, 123
- perindopril
 - dosing and pharmacologic properties 67
 - EUROPA 54, 59, 67, 68, 70, 117, 123
 - PROGRESS 53–4, 66, 68, 92, 94, 95, 96
- peripheral vascular resistance (PVR) 102
- pharyngeal collapse, obstructive sleep apnea 171–8
- phenylephrine, in acute stroke 91
- pioglitazone, effect on endothelial function 12
- plaque characteristics, relationship to morning BP surges 31
- plaque rupture 7
- plasminogen activator inhibitor-1 (PAI-1)
 - expression, effect of reactive oxygen species 5
- platelet endothelial cell adhesion molecule-1 (PECAM-1) 6
- platelets
 - effect of NO 3
 - effect of reactive oxygen species 5
- polysomnography 19
- post-stroke dementia, risk factors 97
- prehypertension, exaggerated morning BP surges 27, 28
- PREVENT (Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial) 117
- primary prevention of CAD 116
 - ACE inhibitors 117, 119
 - ARBs 119
 - calcium channel blockers 117
 - diuretics and beta-blockers 116–17

- ProFESS (Prevention Regimen For Effectively avoiding Second Strokes) 54, 55, 59, 92, 96
- PROGRESS (Perindopril pROtection aGainst REcurrent Stroke Study) 53–4, 66, 68, 92, 94, 95, 96
- dementia risk 97
- proteinuria reduction
- ARBs, relationship to dose 58
 - comparison of ACE inhibitors and ARBs 83
- prothrombotic effects, endothelial dysfunction 6
- proximal aortic diameter, reduced, association with isolated systolic hypertension 106
- pulse pressure (PP) 102
- age-related changes 103, 104
 - association with cardiovascular risk 103
- pulse wave amplification 103, 104
- pulse wave velocity (PWV) 103
- QTc abnormalities, association with morning BP surges 31
- quinapril
- dosing and pharmacologic properties 67
 - effect on endothelial dysfunction (TREND) 11
 - QUIET (Quinapril Ischemic Event Trial) 68, 72, 73–4
- ramipril
- in acute MI (AIRE trial) 67, 68, 70, 73
 - cardiovascular protection
 - HOPE 51–2, 54, 55, 59, 66, 68, 70, 73, 80, 94, 117, 123
 - ONTARGET 58–9, 69, 72, 81, 84, 86, 119 - dose, relationship to BP-independent effects 57–8
 - dosing and pharmacologic properties 67
 - effect on morning BP surges 34
- reactive oxygen species (ROS) 5
- production in diabetes mellitus 8–9
- receptors for advanced glycation end products (RAGE) 9
- recurrent stroke risk, relationship to systolic blood pressure 95, 96
- RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) 80
- renin-angiotensin system (RAS) 7–8, 64–5, 81
- RAS inhibitors
- evidence for benefit beyond BP reduction 51–3
 - in management of morning BP surges 34, 35–6
 - see also* angiotensin-converting enzyme inhibitors (ACEIs); angiotensin-receptor blockers (ARBs)
- renoprotection
- ACE inhibitors 64, 73
 - relationship to dose 57
 - comparison of ACE inhibitors and ARBs 82–4, 86
- resistant hypertension, association with obstructive sleep apnea 19–20
- reverse dipping 46
- reverse white-coat effect 42
- rho kinase 8
- effect of cigarette smoke 9
- rosiglitazone, effect on endothelial function 12
- salt restriction, in isolated systolic hypertension 109
- SAVE (Survival And Ventricular Enlargement) trial 67, 68, 70, 80, 124
- SCOPE (Study on Cognition and Prognosis in the Elderly) 94
- secondary prevention
- benefits of ACE inhibitors 51–2, 53–7, 59–60, 66
 - relationship to dose 57–8
 - high risk CAD patients, comparison of ACE inhibitors and ARBs 58–9
 - of stroke 92–4, 95
 - choice of antihypertensive drug class 96
- self-blood pressure monitoring (SBPM) 41–2, 46, 47, 110–11
- definitions of normal versus hypertensive measurements 45
 - limitations 42–3
 - number of readings 45
 - transtelephonic 45–6
 - types of monitors available 45
 - validation of automated devices 43–5
- sepiapterin 12
- serial median matching 55
- shear stress
- endothelial response 2, 3
 - role of endothelial dysfunction 7
- SHEP (Systolic Hypertension in the Elderly Program) 107, 122

- side-effects, ACE inhibitors 80
 - comparison with ARBs 86, 87
- silent cerebral infarcts, relationship to morning BP surges 28, 30
- simvastatin, CARATS study 10
- sleep disorders *see* central sleep apnea (CSA); obstructive sleep apnea (OSA)
- sleep duration, OSA, relationship to hypertension risk 20–1
- sleep-trough surge 28, 29
- small artery disease, association with morning BP surges 32
- SMILE (Survival of Myocardial Infarction Long-Term Evaluation) study 68, 70–1
- smoking, endothelial dysfunction 9
- smooth muscle cells
 - effect of NO 3
 - effect of reactive oxygen species 5
 - effect of rho kinase 8
 - proliferation in atherosclerosis 7
- SOLVD (Studies Of Left Ventricular Dysfunction) trial 67, 68, 70, 80, 124
- statins
 - CARATS study 10
 - effect on endothelial function 10, 11
 - pleiotropic effects 9–10
- STOP (Swedish Trial in Old Patients)-2 117
- stroke
 - acute
 - hypertension 89, 90–1, 97
 - hypotension 90, 95–6
 - optimal blood pressure 94–5
 - treatment to raise blood pressure 91–2
 - recurrence risk, relationship to systolic blood pressure 95, 96
 - risk factors, early morning BP surges 27, 28, 29
 - risk factors for dementia 97
 - secondary prevention, choice of antihypertensive drug 96
- stroke risk, comparison of ACE inhibitors and ARBs 85, 86
- stroke survivors
 - abnormal blood pressure 92
 - antihypertensive treatment 92–4, 97
- stroke-in-evolution
 - hypotension 95–6
 - optimal blood pressure 94–5
- superoxide anion 5, 7
 - effect of smoking 9
 - production in eNOS uncoupling 4
- superoxide dismutase 5
- sympathetic inhibitors, in treatment of morning BP surges 33, 35
- Syst-China (Systolic Hypertension in China) trial 107
- Syst-Eur (Systolic Hypertension in Europe) trial 107, 117, 122
- systolic blood pressure
 - age-related changes 104
 - coronary heart disease prediction 105
 - target levels 108
 - see also* isolated systolic hypertension (ISH)
- target blood pressure 119–21
 - in acute coronary syndromes 124
 - AHA guidelines 118, 122
 - in isolated systolic hypertension 108
 - achievement 110–11
 - J-curve 121–2
- target organ damage, effect of early morning BP surges 27
- telmisartan
 - cardiovascular protection
 - ONTARGET 58–9, 69, 72, 81, 84, 86, 119
 - TRANSCEND 54, 55, 59, 119
 - effect on morning BP surges 34, 35
- terminal digit preference 39–40
- tetrahydrobiopterin (BH4) 2, 4, 6
 - effect on endothelial function 12
- thiazide diuretics
 - in acute coronary syndromes 124
 - in primary CAD prevention 116–17, 119
- thiazolidinediones, effect on endothelial function 12
- thioredoxin reductase 5
- THOP (Treatment of Hypertension based on Home of Office Blood Pressure) trial 42
- TIBBS (Total Ischemic Burden Bisoprolol Study) 123
- TIBET (Total Ischaemic Burden European Trial) 123
- tissue factor 6
- trandolapril
 - in control of morning BP surges 33
 - dosing and pharmacologic properties 67
 - PEACE 54–5, 72
 - TRACE (Trandolapril Cardiac Evaluation Trial) 68, 70, 124
- TRANSCEND (Telmisartan Randomised Assessment Study in ACE iNtolerant subjects with cardiovascular Disease) 54, 55, 59, 119

- transtelephonic self-blood monitoring of blood pressure 45–6
- TREND (Trial on Reversing Endothelial Dysfunction) 11
- tumour necrosis factor (TNF)-alpha 5
- UKPDS (United Kingdom Prospective Diabetes Study) 122
- unstable angina, management of hypertension 123–4
- valsartan
 - in control of morning BP surges 32
 - effect on morning BP surges 34
 - VALIANT (Valsartan in Acute Myocardial Infarction) trial 69, 72, 124
 - VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) trial 119
- variability of BP, prognostic value 47
- vascular cell adhesion molecule-1 (VCAM-1) 6
- vascular permeability
 - in diabetes mellitus 9
 - effect of reactive oxygen species 5
- vasculogenesis 9
- vasodilation, action of ACE inhibitors 64
- veno-occlusion plethysmography 12
- verapamil, controlled-onset extended-release 33
- von Willebrand factor 6, 13
- waking BP surge 28, 29
- weight reduction
 - in obstructive sleep apnea 22
 - value in isolated systolic hypertension 109
- white-coat hypertension 39, 41, 42
- Wisconsin Sleep Cohort Study 19
- wrist BP devices 45
- xanthine oxidase (XO) 5
- zofenopril, in acute MI (SMILE) 68, 70–1