The Burden of Uncontrolled Hypertension: Morbidity and Mortality Associated With Disease Progression

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Even small elevations above optimal blood pressure values (<120/80 mm Hg) increase the likelihood of developing hypertension (blood pressure ≥140/90 mm Hg) and incurring target organ damage. Until recently, the main emphasis in hypertension treatment had been lowering diastolic blood pressure; however, in the past decade, the important contributions of systolic hypertension, increased pulse pressure, and a blunted reduction in nocturnal blood pressure have been described. Primary hypertension arises from complex, interrelated pathologies. Among the contributors are genetic, environmental, metabolic, vascular, and endothelial factors. Signs of target organ damage herald a poorer prognosis and may present in the heart, blood vessels, kidneys, brain, or eyes. Later consequences include cardiac, cerebrovascular, vascular, and renal morbidities and death. The goal in treating hypertension is to prevent cardiovascular and renal complications. Thus, hypertensive patients with high-normal blood pressure values may benefit from intensive lifestyle interventions to further reduce blood pressure. This is particularly true in patients with additional cardiovascular risk factors. Because of the complex nature of hypertension, it is not surprising that single antihypertensive agents normalize blood pressure for less than a majority of hypertensive patients. Using combination antihypertensive therapy consisting of agents from two or more different antihypertensive drug classes not only increases the likelihood of achieving the target blood pressure goal, but also offers the potential for greater protection against target organ damage by targeting separate pathologic mechanisms.
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The potential for developing hypertension begins in the womb and continues throughout life, offering numerous cues—as well as opportunities for intervention—along the way. It is unclear, in any one individual, which mechanisms initiate the pathway to chronic hypertension. Multiple systems regulate blood pressure, and each system is complex. A positive family history of hypertension or cardiovascular events is associated with a higher risk of hypertension and cardiovascular disease. Low birth weight is known to be associated with adult hypertension.[1] In adults up to approximately age 30, an exaggerated rise in blood pressure during exercise or a resting blood pressure that is higher than normal (<120/80 mm Hg) are associated with an increased likelihood of developing hypertension in middle age. Over a lifetime, untreated hypertension results in an increased burden of premature disability or death from cardiovascular disease.

The hemodynamic hallmark of hypertension is increased peripheral resistance, which can occur through several pathways. Regardless of how the process begins, it appears to either follow or initiate vascular remodeling and hypertrophy in both large and small vessels. Arteriosclerosis is associated with arterial stiffening and loss of vascular compliance, and atherosclerosis is associated with an increasing likelihood of clinical events. Cardiovascular death

occurs through a variety of mechanisms, including occlusion of atherosclerotic vessels or rupture of lesions, resulting in tissue ischemia or infarction in the brain (stroke) or heart (myocardial infarction [MI]); hemorrhage into the brain, resulting in stroke; and cardiac enlargement, resulting in heart failure and/or sudden death. Other major consequences of chronic hypertension include kidney failure and retinopathy (Table I).

CHARACTERISTICS OF BLOOD PRESSURE

An awareness of the characteristics and variability of blood pressure is essential for proper diagnosis and optimal management of hypertension. The positive relationship between increasing cardiovascular risk and higher blood pressure level is continuous. Evidence of risk at lower levels of blood pressure has accrued during recent years, changing our understanding of what truly represents optimal blood pressure levels. Diastolic blood pressure (DBP) is now less emphasized than systolic blood pressure (SBP), while pulse pressure (the difference between SBP and DBP) has been highlighted as an important prognostic indicator. Blood pressure variability, emanating from a variety of sources, may result in an individual being inappropriately labeled hypertensive or normotensive. For this reason, proper measurement technique is crucial for correct diagnosis and management of hypertension. Characteristics of blood pressure variability also offer important clues regarding the individual's underlying pathology and cardiovascular risk.

Table I. Potential Complications and Medical Procedures Associated With Hypertension

Cardiac
Left ventricular hypertrophy
Heart failure
Angina pectoris
Myocardial infarction
Coronary revascularization procedures
Stenting
Diagnostic cardiac catheterizations
Cerebrovascular
Transient ischemic attacks
Vascular dementia
Stroke (ischemic, hemorrhagic)
Hypertensive encephalopathy
Renal
Microalbuminuria and proteinuria
Nephrosclerosis
Renal failure and end-stage renal disease
Dialysis
Kidney transplantation
Other/macrovascular
Abdominal aortic aneurysm
Aortic dissection
Peripheral arterial disease
Other/microvascular
Hypertensive retinopathy

The Impact of DBP, SBP, and Pulse Pressure

SBP continues to rise with age, while DBP plateaus at about age 55 and declines thereafter. Therefore, pulse pressure tends to increase after age 55. Both elevated SBP and increased pulse pressure are indicative of structural and functional damage to large vessels. The typical age-related arteriosclerotic changes in the large vessels—resulting in arterial stiffness and decreased compliance—are substantially accelerated by chronic hypertension.[2]

Reductions of both DBP and SBP have a powerful effect in reducing cardiovascular events. He and Whelton[3] assessed data from 10 randomized clinical trials, involving more than 18,000 participants, and found that an average reduction of 12–13 mm Hg in SBP over 4 years resulted in reductions of 21% in coronary heart disease (CHD), 37% in stroke, 25% in total cardiovascular mortality, and 13% in all-cause mortality. Data from the Systolic Hypertension in the Elderly Program (SHEP) study[4] and the Systolic Hypertension in Europe (Syst-Eur) trial[5] demonstrated that treating isolated systolic hypertension (ISH) in elderly hypertensive patients also resulted in marked reduction in the rates of MI, heart failure, and stroke.

It is relevant to ask which determinant—SBP, DBP, or pulse pressure—is most predictive of cardiovascular risk. Data from the large Multiple Risk Factor Intervention Trial (MRFIT) cohort[6] showed conclusively that over approximately 11 years of follow-up, higher SBP was related to increased risk of CHD in a continuous manner, independent of DBP. The pooled data analyzed by He and Whelton[3] also indicated that CHD, stroke, all-cause death, and end-stage renal disease were more strongly associated with SBP than DBP. There is a growing body of information that advocates using pulse pressure for defining risk as well. Franklin and colleagues[7] evaluated data from the Framingham Heart Study and found that neither initial SBP nor DBP were superior to pulse pressure in predicting risk for CHD; although in the same database, SBP and pulse pressure were found to be stronger predictors of cardiovascular risk for older individuals, while DBP was found to be a stronger predictor for younger (age <50 years) individuals.[8]

Classification of blood pressure stages based on the seventh report of the Joint National Committee

on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[9] are shown in Table II. In 1999, Lloyd-Jones and colleagues[10] analyzed blood pressure measurements obtained from about 3600 subjects in the Framingham Heart Study, and found that more than one third had SBP and DBP values that did not match JNC VI staging. This led to almost a third of this group having their stage increased on the basis of their SBP, but only 4% being up-staged on the basis of their DBP. Thus, 91% of subjects were correctly classified according to JNC VI blood pressure stage by SBP alone, while only 22% were correctly classified by DBP. The percentage of subjects whose stage was correctly identified by SBP alone increased to 99% in individuals older than 60 years of age.

Concerns regarding SBP are also relevant to blood pressure management. ISH (defined as SBP ≥140 mm Hg and DBP <90 mm Hg) is common, especially in individuals aged ≥60 years. Yet despite the proven benefits of SBP reduction, only 25% of patients with ISH are adequately controlled.[11] SBP has generally been less well controlled than DBP, both in clinical settings and in randomized, controlled clinical trials such as MRFIT[12] and the Hypertension Optimal Treatment (HOT) trial,[13] where DBP control rates were >90%, but SBP control rates were <60%. To draw greater attention to this problem, a clinical advisory statement was issued in 2000 from the Coordinating Committee of the National High Blood Pressure Education Program (NHBPEP) urging that SBP become the major criterion for diagnosis, staging, and management of hypertension, particularly in middle-aged and older Americans.[14] More recently, SBP control rates of at least 67% have been reported from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[15] and the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial.[16] For those not controlled in ALLHAT, approximately 50% had SBPs between 140 and 149 mm Hg but more than two thirds did not have medication doses increased or available medications added, suggesting that even better control should be achievable.

Blood Pressure Variability

Blood pressure variability is a necessary homeostatic property; it demonstrates both individual and population characteristics and is affected by age, sex, regional variation, and genetic features. Physiologic variation occurs as a result of central and sympathetic regulation, reflex mechanisms, emotions and activities, blood viscosity, and other influences such as insulin, endothelin, and angiotensin II.[17] Sources of individual variability in blood pressure measurements may be random or persistent, and include diurnal variation, measurement errors, activity before measurement, position during measurement, location (i.e., clinic or home), and propensity for the phenomenon of "white-coat" hypertension.

Diurnal and seasonal variation in blood pressure is universal. Upon rising and becoming active, SBP typically rises by as much as 20–25 mm Hg, and DBP by 10–15 mm Hg. Both SBP and DBP are highest late in the afternoon; they decrease when an individual is in the recumbent position, and are lowest during sleep.[18] Abnormal diurnal variation is associated with increased cardiovascular risk. The onset of morning activity, with the resulting surge in blood pressure and catecholamine release, may act as a trigger for cardiovascular events such as sudden cardiac death, MI, unstable angina, and stroke—all of which occur more frequently in the early morning (following arising from sleep) than at other times of the day.[19]

Within the pattern of normal diurnal variation, smooth, 24-hour blood pressure control is considered clinically important, and lack of this type of control may increase the risk of target organ damage (TOD) and cardiovascular events.[9] Some investigators have demonstrated that the severity of

Table II. Classification of Blood Pressure*

CATEGORY	SBP (MM HG)		DBP (MM HG)
Normal	<120	And	<80
Prehypertension	120–139	Or	80–89
Hypertension, stage 1	140–159	Or	90–99
Hypertension, stage 2	≥160	Or	≥100

SBP=systolic blood pressure; DBP=diastolic blood pressure; *treatment determined by highest blood pressure category
Data derived from the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) 2003[9]

hypertension TOD is more closely related to mean 24-hour ambulatory blood pressure measurements than to random clinic measurements,[20] and that greater 24-hour blood pressure variability also correlates with increased TOD, such as left ventricular hypertrophy (LVH).[21]

A persistent pattern of nighttime blood pressure levels that drop <10% below daytime levels is termed "nondipping." This phenomenon closely correlates with TOD and LVH in particular.[22–24] Bianchi and colleagues[25] found that hypertensive patients who were nondippers had higher median urinary albumin excretion (42 mg/24 hour) compared with dippers (17.5 mg/24 hour), suggesting a different pattern of renal involvement in nondippers. On the other hand, too great a decline in blood pressure during sleep, so-called "extreme dipping" (>20% from daytime levels), particularly in elderly hypertensive patients, may increase the risk of silent cerebral infarcts.[26]

Because of the data implicating blood pressure variability with severity of hypertension and TOD, some experts recommend greater use of 24-hour ambulatory blood pressure measurements in defining the severity of hypertension and believe that reduction of wide blood pressure fluctuations should be one of the goals of antihypertensive therapy.[17] However, this has not been established, as virtually all large epidemiologic studies demonstrating the relationship between blood pressure and clinical outcomes, and clinical trials showing the benefits of antihypertensive drug treatment, have relied on carefully measured clinic blood pressure readings.

PATHOGENESIS OF HYPERTENSION

An understanding of the pathologic pathways that contribute to hypertension is critical to developing successful blood pressure management strategies in the areas of drug development and design of clinical trials. However, a number of factors may contribute to high blood pressure in any given individual, including a mix of genetic elements; environmental considerations (e.g., diet, smoking, alcohol, exercise); metabolic factors; vascular responses; activity of the renin-angiotensin system (RAS) and the sympathetic nervous system (SNS); sodium sensitivity; and endothelial functions.

Genetic Models

Depending on the population studied, estimates regarding the inheritability of hypertension vary from as low as 15% to as high as 70%.[27] Early genetic research was successful in identifying genetic loci for familial transmission of cardiovascular diseases (e.g., a defect in the gene for the low-density lipoprotein cholesterol receptor site associated with familial hypercholesterolemia was recognized in the 1970s). More recent developments have highlighted the theory that primary hypertension is most likely the cumulative result of the small effects of a large number of "normal" genes adversely interacting with the contemporary environment. The effect of environment should not be underestimated. In fact, almost all individuals living in developed countries may develop hypertension if they live long enough; whereas, in isolated environments, very few presumably similarly predisposed individuals who are lean and physically very active, and/or who have limited access to salt, develop hypertension. Currently, however, a broad effort is aimed at searching for allelic differences in a variety of genes associated with blood pressure regulation.

Preclinical research into gene therapy for hypertension has involved transferring DNA into cells by a variety of delivery methods through either a normal (sense) or reverse (antisense) approach, using genetic targets such as kallikrein, atrial natriuretic peptide, angiotensin-converting enzyme (ACE), and angiotensinogen.[28] To date, genetic variants of key components of the RAS have been studied most extensively.[29–31] In the future, identification of specific genetic markers may help physicians target high-risk individuals for prevention, early intervention, and possibly selection of drug therapy, particularly if it can be demonstrated that specific classes of antihypertensive agents more reliably prevent cardiovascular or renal outcomes in specific groups of individuals.

Vascular and Cardiac Responses

The heart and large blood vessels are pathologically involved at the onset of hypertension: the heart can be viewed as one of several initiators of hypertension, and hypertension, in turn, is a factor capable of damaging the heart. Initial studies have suggested that one of the earliest signs of hypertension is an increase in total peripheral resistance. This is currently viewed as the clinical hallmark of primary hypertension. Some studies have also indicated that in young individuals, an early finding associated with high blood pressure is an increase in cardiac output, which is likely to be related to increased SNS activity.[32]

Both with aging and in hypertension, cardiac output decreases in association with decreased left ventricular compliance, but in hypertension, this is exacerbated by increased afterload. Eventually, cardiac structural changes, such as increased left ventricular mass, occur to meet the demands of an

increased cardiac workload.[33] LVH, in association with left ventricular dysfunction (both systolic and diastolic), is common in patients with chronic high blood pressure and contributes an added independent risk of CHD, heart failure, stroke, peripheral arterial disease, and sudden cardiac death.[34]

With aging or hypertension, the large arteries undergo a variety of structural changes, including smooth muscle cell hypertrophy and collagen deposition, which together lead to loss of elasticity and reduced compliance; systolic hypertension and a widened pulse pressure is often the result. Stiffening of the arteries also increases pulse wave velocity and flow turbulence. Pulse wave contour analyses show a steady decline in arterial compliance with aging.[2]

Early studies found a limited correlation between the level of blood pressure and left ventricular mass, although ambulatory blood pressure measurements correlate to a greater degree with LVH than do clinic measurements.[34] Regression of LVH has been demonstrated to occur with blood pressure reduction. Total blood pressure load, defined as the percentage of time that blood pressure is above a specific threshold (such as 140/90 mm Hg), may be a better indicator of the propensity to develop LVH than random blood pressure measurements or mean 24-hour ambulatory blood pressure measurements. Mulé and colleagues[35] found that calculated SBP load (based on the percentage of ambulatory blood pressure measurements exceeding 140 mm Hg while awake and 120 mm Hg while asleep) was a better predictor of left ventricular wall thickness and reduced mid-wall fractional shortening than 24-hour mean SBP.

Atherosclerosis: A Response to Injury

The vascular endothelium is prone to injury from many sources. High arterial pressure may cause damage due to increased shear stress. Harm to the vessel wall results in subendothelial exposure to numerous cell types that are capable of stimulating inflammation, platelet adherence, release of growth factors, and replication of smooth muscle

Table III. Cell Types Involved in Atherosclerotic Lesions

Cell Types Involved	Activities	Events	AHA Classification
Endothelium	Oxidize LDL	Endothelial injury	None
Platelets	Produce PDGF, which has strong chemoattractant and mitogenic effect on SMC	Endothelial injury	None
T-lymphocytes	Infiltrate into subendothelium	Endothelial injury	None
Monocytes Macrophages Foam cells	Adhesion Migrate into media Ingest oxidized LDL Formation of foam cells Stimulate migration and proliferation of SMC & connective tissue	Formation of fatty streak containing mostly lipid-filled macrophages May progress or regress	Fatty streak (I-III)
SMCs Monocytes Macrophages	Migrate into media Stimulate proliferation of SMC & connective tissue	Thickening of intima	Diffuse intimal thickening (IV)
SMCs Platelets	Migrate from media to intima Role in plaque growth	Fibrous plaque formation Complicated lesions with hemorrhage, thrombosis or calcification	Fibrous plaque (V and VI)
SMCs Platelets T-lymphocytes	Accumulation in advanced atherosclerosis Role in acute coronary syndromes Cytokines from activated T-lymphocyte cells may be involved in plaque rupture within lesions	Plaque rupture Can provoke unstable angina, MI Thrombus may become organized into lesion	

AHA=American Heart Association; LDL=low-density lipoprotein cholesterol; PDGF=platelet-derived growth factor; SMC=smooth muscle cell; MI=myocardial infarction

cells in the process of repair. The types of cells involved in the formation of atherosclerotic lesions are described in Table III.

Atherosclerotic plaque forms in the intima of large vessels. Such plaques can acutely rupture or gradually organize into occlusive lesions. In smaller vessels, hypertrophy, hyperplasia, and fibrosis may lead to widespread vascular occlusion. Atherosclerosis of the coronary arteries reduces the blood supply to the myocardium; this can result in acute and/or chronic ischemia resulting in MI, sudden cardiac death, or ischemic cardiomyopathy.

Abnormalities of platelet function, coagulation, and fibrinolysis following endothelial injury constitute the prothrombotic or hypercoagulable state that is characteristic of hypertension. This prothrombotic state is independently associated with an increased likelihood of LVH, increased risk of stroke and thromboembolism in patients with atrial fibrillation, and a worse long-term prognosis.[36–39] Other potential markers for risk have also been identified. Plasma levels of endothelin-1, a potent endothelial-derived vasoconstrictor, are higher in hypertensive patients compared with normotensive control patients. Increased endothelin-1 levels are believed to be one of several neurohumoral substances that contribute to the increased peripheral resistance in hypertensive patients.[40]

Renal Regulation

Normally, increases in blood pressure trigger a phenomenon known as pressure natriuresis, in which the kidneys excrete sufficient sodium and water to return blood pressure to its original set point. There is a resetting of this mechanism to a higher blood pressure level to maintain sodium balance under conditions of sustained increases in arterial pressure. Low volume states and/or decreases in total body sodium trigger renin release, a process which will then serve to activate downstream components of the RAS and, in particular, increase plasma concentrations of angiotensin II and aldosterone.

Renin-Angiotensin System. The RAS has been extensively studied both in animals and humans, in tissues and cell cultures, and it has been characterized by genetic mapping. Renin is the precursor to angiotensin I, which is transformed to angiotensin II (Ang II) by ACE. Ang II is capable of a wide range of actions throughout the body. In its blood pressure regulatory role, Ang II is a potent vasoconstrictor, causes sodium and water retention, and induces thirst. There are two major Ang II receptors: AT_1 and AT_2. Ang II acts widely throughout the body at AT_1 receptor sites in the kidneys, adrenal glands, heart, blood vessels, and brain. Agents that block the production of Ang II (ACE inhibitors) and agents that block the action of Ang II (Ang II AT_1 receptor blockers [ARBs]) have demonstrated the ability to improve the prognosis for patients with diabetic nephropathy and renal insufficiency.[41–46]

In addition to its role in blood pressure regulation, Ang II has local trophic effects that can contribute to heart and/or renal failure. ACE inhibitors, and more recently, ARBs, have demonstrated significant benefits in patients with heart failure.[47,48] Other potentially atherogenic effects related to the overexpression of Ang II at AT_1 receptor sites are also hypothesized.[49] The role of the AT_2 receptor in the pathophysiology of end organ disease is also being investigated; animal studies have demonstrated that AT_2 receptor stimulation opposes cell growth, potentially countering AT_1 effects.[40] This may have important clinical implications, as ACE inhibitors and ARBs work through different mechanisms: ACE inhibitors limit the production of Ang II, while ARBs block its access to AT_1 receptors. Further, when ARBs block the AT_1 receptor they interrupt a short feedback loop with a resultant increase in Ang II levels. This rise in Ang II with ARB therapy can stimulate AT_2 receptors, although the clinical benefit of this remains to be determined. The use of combination therapy with ACE inhibitors and the ARB valsartan has recently been reported in patients with heart failure.[48] The results of these studies offer some promise for an additional novel treatment for heart failure.

Salt Sensitivity. It is estimated that approximately one half of all hypertensive patients have some degree of salt sensitivity, defined as a 10 mm Hg drop in blood pressure when consuming a low-salt vs. a high-salt diet.[50] The mechanisms for salt sensitivity are not entirely clear. It has been suggested that salt sensitivity occurs due to defects in cellular sodium transport, which are variably contributed to by abnormalities in the RAS and SNS.[50,51] Low plasma renin activity is often associated with hypervolemia and salt sensitivity; however, the case for identifying two distinct groups of hypertensive patients—low-renin and high-renin—for the purpose of differential treatment has not been convincingly established.

Salt sensitivity is associated with a wide range of abnormalities, including increases in SBP, glomerular hydraulic pressures, microalbuminuria, LVH, and total cholesterol levels, as well as a blunted nocturnal decline in blood pressure.[50,51] Bragulat and de La

Sierra[52] have also found that salt sensitivity was associated with endothelial dysfunction in a small group of hypertensive patients (N=26), and Galletti and colleagues[53] found that insulin resistance was independently associated with salt sensitivity in a cohort of hypertensive patients (N=99). Some investigators have proposed that salt sensitivity is an independent cardiovascular risk factor.[54]

Interestingly, the strongest association with salt sensitivity noted thus far appears to be LVH.[51,54–56] In a retrospective follow-up of 156 Japanese hypertensive patients who had earlier been evaluated for salt sensitivity, Morimoto and colleagues[54] found that the salt-sensitive group had a significantly greater likelihood of having LVH than did the salt-resistant group (38% vs. 16%).

Metabolic Syndrome

The metabolic syndrome, also known as the insulin resistance syndrome, is characterized by hyperinsulinemia, central obesity, and atherogenic dyslipidemia pattern (elevated triglycerides and low-high-density lipoprotein). Many individuals with the metabolic syndrome will eventually develop type 2 diabetes. If these patients are also hypertensive, their risk of cardiovascular events is profoundly increased.

The interrelationships among obesity, impaired glucose tolerance, hypertension, and dyslipidemia have provided ample material for inquiry regarding a range of adverse outcomes. Substantial evidence links insulin resistance to accelerated atherogenic damage and adverse cardiovascular outcomes, and elevated levels of circulating insulin may be implicated in several untoward effects, including stimulation of SNS activity, increased renal sodium reabsorption, and elevated levels of plasminogen activator inhibitor-1.[57]

Neurohormonal Regulation

The SNS is activated during activity and stress, with resulting rapid increases in heart rate and cardiac output. Hypertensive individuals generally have increased sympathetic activity, which also greatly increases the risk of heart failure and diabetes.[58] Sustained tachycardia may also present a risk for endothelial injury, thus contributing to atherogenesis. In the San Antonio Heart Study cohort,[59] a hyperdynamic state (defined as the highest quartile for pulse pressure and heart rate) was associated with higher body mass index, higher fasting and 2-hour postprandial blood glucose levels, and was predictive for the development of type 2 diabetes. In the Framingham Heart Study,[60] sustained increased heart rate was significantly and independently related to sudden cardiac death. However, not all studies have shown these associations. Dopamine, the precursor for both epinephrine and norepinephrine, also plays an important role in blood pressure regulation and renal function, by influencing the central and peripheral nervous systems and by its interactions with the RAS.[61]

Adrenergic blockade, with centrally acting agents, such as clonidine, or with α and β blocking agents, was one of the earliest approaches to controlling blood pressure and remains a successful form of adjunctive therapy. Beta blockers (without intrinsic sympathomimetic activity) are indicated for patients post-MI, because they have been shown to reduce the risk for subsequent MI or sudden cardiac death.[9]

DISCUSSION

Hypertension may lead to untoward consequences in the heart, brain, vasculature, kidneys, or eyes. Chronic high blood pressure results in an acceleration of atherosclerosis, CHD, heart failure, and renal failure. The higher the pressure, the more likely these various diseases will develop. If untreated, approximately one half of all hypertensive patients will develop heart failure, and a majority will die prematurely of cardiovascular or renal disease.[62]

This review of pathophysiologic processes associated with the development and progression of hypertension is brief compared with the available data and hypotheses available for review—a storehouse of reading material that is far more than any clinician could possibly digest. The intention here is to underscore the complexities and interrelatedness of hypertension and cardiovascular diseases, which have such enormous potential to do harm if not properly managed. The treatment of hypertension is covered in another review in this Supplement[63]; however, it is quite clear that a variety of factors must be taken into account to optimally treat patients with, or at risk of, hypertension.

With these considerations in mind, the following recommendations seem appropriate. Foremost, the goal in treating high blood pressure is to prevent TOD, and in particular, cardiovascular and renal morbidity and mortality. A thorough cardiovascular risk assessment of patients (hypertensive or not) and a staunch resolve to promote therapeutic lifestyle changes are critical, but often omitted, tasks in too many clinical settings.

Lowering blood pressure to the relevant target goal is the ultimate objective of pharmacologic therapy. Most patients will require at least two antihypertensive medications to achieve goal blood pressure.[15] In general, lower blood pressure levels are associated with less risk in both high-risk and low-risk hypertensive popu-

lations.[13,64] Because hypertension occurs through more than one, and often multiple, pathologic pathways, combination therapy may be advantageous, as it targets more than one of these defects. The recently completed ALLHAT trial has demonstrated that diuretics should be included in the initial regimen for most hypertensive patients, but RAS-blocking agents (ACE inhibitors and ARBs) should also be included in the regimen for patients with heart failure and diabetic or hypertensive nephropathy, and either RAS-blocking agents or β blockers should be included in the antihypertensive drug regimens for patients post-MI.[9,65] In addition to diuretics, calcium channel blockers and RAS-blocking agents are also appropriate agents for treating ISH, because they both effectively reduce blood pressure and improve arterial compliance parameters in patients with vascular stiffness.[5,11,66]

SUMMARY

The major goal of the clinical management of hypertension—bringing blood pressure down to an appropriately selected target level—will generally require more than one medication. Combinations of antihypertensive medications that succeed in bringing blood pressure to goal decrease the risk for the catastrophic consequences of chronically elevated blood pressure by counteracting more than a single pathophysiologic pathway associated with hypertension.

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