Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Circulation 2007;115;2761-2788; originally published online May 14, 2007;
DOI: 10.1161/CIRCULATIONAHA.107.183885
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

AHA Scientific Statement

Treatment of Hypertension in the Prevention and Management of Ischemic Heart Disease

A Scientific Statement From the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention

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Epidemiological studies have established a strong association between hypertension and coronary artery disease (CAD). Hypertension is a major independent risk factor for the development of CAD, stroke, and renal failure. The optimal choice of antihypertensive agents remains controversial, and there are only partial answers to important questions in the treatment of hypertension in the prevention and management of ischemic heart disease (IHD), such as:

- What are the appropriate systolic blood pressure (SBP) and diastolic blood pressure (DBP) targets in patients at high risk of developing CAD or in those with established CAD?
- Are the beneficial effects of treatment simply a function of blood pressure (BP) lowering, or do particular classes of drugs have uniquely protective actions in addition to lowering BP?
- Are there antihypertensive drugs that have shown particular efficacy in the primary and secondary prevention of IHD?
- Which antihypertensive drugs should be used in patients who have established CAD with stable or unstable angina pectoris, in those with non–ST-elevation myocardial infarction (NSTEMI), and in those with ST-elevation myocardial infarction (STEMI)?

This scientific statement summarizes the published data relating to the treatment of hypertension in the context of CAD prevention and management and attempts, on the basis of the best available evidence, to develop recommendations that will be appropriate for both BP reduction and the management of CAD in its various manifestations. Where data are meager or lacking, the writing group has proposed consensus recommendations, with all of the reservations that that term implies and with the hope that large gaps in our knowledge base will be filled in the near future by data from well-designed prospective clinical trials.

All of the discussion and recommendations refer to adults. The writing committee has not addressed hypertension or IHD in the pediatric age group. Also, there is no discussion of the different modes of assessing BP, including 24-hour ambulatory BP monitoring. These were the subject of an American Heart Association (AHA) scientific statement in 2005.[1]

A classification of recommendation and level of evidence have been assigned to each recommendation, according to the AHA format as follows:

Classification of Recommendations:

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on April 9, 2007. A single reprint is available by calling 800-242-8721 (US only) or writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0412. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

This statement has been copublished in *Hypertension.*

Expert peer review of AHA Scientific Statements is conducted at the AHA National Center. For more on AHA statements and guidelines development, visit http://www.americanheart.org/presenter.jhtml?identifier=3023366.

(*Circulation.* 2007;115:2761-2788.)

***Circulation* is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.107.183885**

TABLE. Summary of Main Recommendations

Area of Concern	BP Target, mm Hg	Lifestyle Modification†	Specific Drug Indications	Comments
General CAD prevention	<140/90	Yes	Any effective antihypertensive drug or combination‡	If SBP ≥160 mm Hg or DBP ≥100 mm Hg, then start with 2 drugs
High CAD risk*	<130/80	Yes	ACEI or ARB *or* CCB *or* thiazide diuretic *or* combination	If SBP ≥160 mm Hg or DBP ≥100 mm Hg, then start with 2 drugs
Stable angina	<130/80	Yes	β-Blocker *and* ACEI or ARB	If β-blocker contraindicated, or if side effects occur, can substitute diltiazem or verapamil (but not if bradycardia or LVD is present)
				Can add dihydropyridine CCB (not diltiazem or verapamil) to β-blocker
				A thiazide diuretic can be added for BP control
UA/NSTEMI	<130/80	Yes	β-Blocker (if patient is hemodynamically stable) *and* ACEI or ARB§	If β-blocker contraindicated, or if side effects occur, can substitute diltiazem or verapamil (but not if bradycardia or LVD is present)
				Can add dihydropyridine CCB (not diltiazem or verapamil) to β-blocker
				A thiazide diuretic can be added for BP control
STEMI	<130/80	Yes	β-Blocker (if patient is hemodynamically stable) and ACEI or ARB§	If β-blocker contraindicated, or if side effects occur, can substitute diltiazem or verapamil (but not if bradycardia or LVD is present)
				Can add dihydropyridine CCB (not diltiazem or verapamil) to β-blocker
				A thiazide diuretic can be added for BP control
LVD	<120/80	Yes	ACEI or ARB *and* β-blocker *and* aldosterone antagonist¶ *and* thiazide or loop diuretic *and* hydralazine/isosorbide dinitrate (blacks)	Contraindicated: verapamil, diltiazem, clonidine, moxonidine, α-blockers

UA indicates unstable angina; LVD, LV dysfunction; and ACEI, ACE inhibitor.

Before making any management decisions, you are strongly urged to read the full text of the relevant section of the scientific statement.

*Diabetes mellitus, chronic kidney disease, known CAD or CAD equivalent (carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm), or 10-year Framingham risk score ≥10% (see Appendix).

†Weight loss if appropriate, healthy diet (including sodium restriction), exercise, smoking cessation, and alcohol moderation.

‡Evidence supports ACEI (or ARB), CCB, or thiazide diuretic as first-line therapy.

§If anterior MI is present, if hypertension persists, if LV dysfunction or HF is present, or if the patient has diabetes mellitus.

¶If severe HF is present (New York Heart Association class III or IV, or LVEF <40% and clinical HF). See text.

Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence:

Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses.

Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies.

Level of Evidence C: Only consensus opinion of experts, case studies, or standard of care.

The general design of the scientific statement is based on the concept that each of the clinical sections refers to a particular subset of patients, so that each section should provide a "stand-alone" description of the recommendations and their justification, independent of the other sections. This should make it easier for practitioners to extract the information relevant to any particular patient, without needing to cross-reference, and we hope it will thereby increase the utility of the document. With this organization, there may be some repetition of information from one section to the next, but we have tried to keep that to a minimum. A summary of the main recommendations is presented in the Table.

Epidemiology of Hypertension and CAD

Hypertension is a major independent risk factor for CAD, stroke, and renal failure. The latest version of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[2] recommendations has defined "hypertension" as a BP of ≥140/90 mm Hg. At this cutoff value, at least 65 million adult Americans, or nearly one fourth of the adult population of the United States, have hypertension. Another one fourth of the population is in the "prehypertension" range, defined as an SBP of 120 to 139 mm Hg or a DBP of 80 to 89 mm Hg.

There is a strong but complex association of BP and age. Until about 50 years of age, SBP and DBP rise in tandem. After age 50 years, SBP continues to rise steadily, whereas DBP tends to fall. The prevalence of systolic hypertension is thus directly proportional to the age of the population, and more than half of Americans over age 65 years have isolated systolic or combined systolic-diastolic hypertension. In contrast, the prevalence of diastolic hypertension diminishes, and fewer than 10% of individuals over the age of 65 years have diastolic hypertension. The Framingham Heart Study has estimated the 20-year risk of developing hypertension as >90% for men and women not yet hypertensive by middle age (55 to 65 years of age).[3] There is also an enhanced risk for cardiovascular events associated with increased pulse pressure; this is discussed more fully in the section on "Primary Prevention of CAD in Hypertension: Observational Studies."

There is a change with age in the relative importance of SBP and DBP as risk indicators. Below age 50 years, DBP is the major predictor of IHD risk, whereas above age 60, SBP is more important.[4] Because the prevalence of hypertension increases with age, adequate control of both SBP and pulse

pressure rather than DBP in the elderly has become the dominant public health imperative. However, nearly all of the epidemiological and clinical trial data concerning outcomes have been based on SBP and/or DBP, so there are few if any data on the efficacy of antihypertensive drugs as a function of pulse pressure. Also, at all ages, the relationship between SBP or DBP and IHD mortality is consistent, robust, and continuous, with no apparent threshold value. In a meta-analysis of 61 studies that included almost 1 million adults, BP was related to fatal IHD over the BP range of 115/75 to 185/115 mm Hg. Overall, each increase in SBP of 20 mm Hg (or 10 mm Hg in DBP) doubles the risk of a fatal coronary event. Absolute risk of these adverse outcomes also increases with age, such that for any given SBP, the risk of fatal CAD was ≈16-fold higher for persons 80 to 89 years of age than for those 40 to 49 years of age.[5] In the Chicago Heart Association Detection Project in Industry, men 18 to 39 years of age at baseline with a BP of 130 to 139/85 to 89 mm Hg or with stage 1 hypertension (140 to 159/90 to 99 mm Hg) accounted for nearly 60% of all excess IHD, overall cardiovascular disease, or all-cause mortality.[6] 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.[7]

Effects of Treatment

The risk of cardiovascular disease in the patient with hypertension can be greatly reduced with effective antihypertensive therapy. The major reductions in cardiovascular morbidity and mortality over the past 50 years have been attributed mainly to the increased availability and utilization of various drug treatments for hypertension. Randomized trials have shown that BP lowering produces rapid reductions in cardiovascular risk[8] that are highly consistent with predictions of risk reduction that can be inferred from observational studies. For example, a 10-mm Hg–lower usual SBP (or a 5-mm Hg–lower usual DBP) would predict a 50% to 60% lower risk of stroke death and an approximately 40% to 50% lower risk of death due to CAD or other vascular causes at middle age, benefits that are only slightly less in older people.[5] However, there are data to show in very old individuals, those at least 85 years of age, that the association between high BP and mortality is weaker[9] and that lowering BP in patients older than 80 years reduces stroke but not nonstroke (including coronary) deaths.[10]

Several studies (HOPE [Heart Outcomes Prevention Evaluation], SAVE [Survival And Ventricular Enlargement], and EUROPA [EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease]; see below) have shown a beneficial effect of angiotensin-converting enzyme (ACE) inhibitors on cardiovascular outcomes in individuals, some hypertensive and some not but all with established cardiovascular disease or with high risk for the development of cardiovascular disease. However, we do not yet have any outcome studies of treatment of "prehypertension" in individuals with BPs in the range of 130 to 139/80 to 89 mm Hg. The only prospective clinical trial of BP reduction in individuals with "normal" BPs is the TROPHY (TRial Of Preventing HYpertension) study,[11] in which subjects with an SBP of 130 to 139 mm Hg or a DBP of 85 to 89 mm Hg were randomized to be treated for 2 years with either the angiotensin receptor blocker (ARB) candesartan or placebo and followed up for an additional 2 years. Hypertension developed in significantly more participants in the placebo group (two thirds of this cohort at 4 years) than in the candesartan group, with a relative risk reduction of 66.3% at 2 years and 15.6% at 4 years. However, the study was not designed or powered to assess cardiovascular outcomes.

Risk Factor Interactions

Data from the Framingham Heart Study have provided evidence supportive of an interrelationship between hypertension, dyslipidemia, glucose intolerance, cigarette smoking, and left ventricular (LV) hypertrophy.[12] These 5 primary risk factors are the most important reversible determinants of cardiovascular risk and appear to operate independently of one another, although it appears that the risk increases in a multiplicative rather than simply additive fashion. This has led to the idea that the threshold at which a patient should be treated for hypertension, as well as the goal to which he/she should be treated, is lowered in those at high risk for cardiovascular disease by virtue of the presence of other risk factors. In the guidelines developed by the National Kidney Foundation,[13] this principle has been followed for patients with albuminuria and even modest chronic renal insufficiency, for which the BP threshold for the institution of antihypertensive therapy is 130/80 mm Hg. The American Diabetes Association,[14] the National Kidney Foundation,[13] and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[2] all agree that the BP goal of treatment in individuals with diabetes mellitus or with chronic kidney disease should be <130/80 mm Hg, a lower goal than that recommended for other hypertensive patients (<140/90 mm Hg).

There is also a correlation between hypertension and body mass, and both are strongly correlated with CAD. Hypertension and abdominal obesity are components of a larger risk factor constellation of cardiovascular risk factors, the "metabolic syndrome," which also includes a characteristic form of dyslipidemia (high triglycerides and low high-density lipoprotein cholesterol), and an elevated fasting blood glucose level.[15]

Mechanisms of Hypertension and CAD

The diffuse arteriosclerosis of hypertension, the more patchy atherosclerotic lesions of epicardial CAD, and the remodeling of medium and small coronary arteries may all have common pathophysiological mechanisms. Prevention and reversal of these processes are major goals of therapy for hypertension, CAD, and ischemic heart failure (HF).

Physical Forces and Hemodynamics

In hypertension, there is both an increased myocardial oxygen demand and a diminished coronary blood flow or, at least, a diminished coronary flow reserve. The increased demand is due to the increased LV output impedance, which raises intramyocardial wall tension, as well as to LV hypertrophy if

present. The diminished coronary flow reserve is a complex function of the plaque-related occlusive CAD, remodeling of medium and small coronary arteries, and, if the diastolic pressure is low enough, a decrease in coronary perfusion pressure.

Physical forces (pressure and flow) are the primary determinants of cardiac structure and function and also influence vascular remodeling and atherosclerosis. When SBP is elevated, there is an increase in both LV output impedance and intramyocardial wall tension, which increase myocardial oxygen demand. The wide pulse pressure and systolic hypertension in older individuals are almost always due to inappropriately high aortic impedance, which results from decreased aortic diameter or increased effective stiffness due to aortic wall thickening or changes in wall composition. Aging is associated with thinning and fragmentation of vascular elastin together with increased collagen deposition; this degenerative process is more pronounced in individuals with sustained systolic hypertension.

SBP is not constant within the arterial tree because of structural and functional variation in properties related to wave propagation and wave reflection. Central SBP is particularly influenced by pressure wave reflection, which in turn increases with age and structural changes in arteries. Increased wave reflection leads to central systolic pressure augmentation, which increases LV pressure load and cardiac work. These in turn may cause angina pectoris and LV hypertrophy.

Systolic Hypertension

In persons who have elevated or high-normal BP at an early age, the increased vascular wall tension leads to thinning, fragmentation, and fracture of elastin fibers, as well as increased collagen deposition in arteries, which results in decreased compliance of these vessels. In addition to these structural abnormalities, endothelial dysfunction, which develops over time as a consequence of both aging and hypertension, contributes functionally to increased arterial rigidity in elderly persons with a widened pulse pressure and subsequent isolated systolic hypertension.[16] Increased arterial stiffness, with related increases in pulse wave velocity and reflection, leads to augmentation of central SBP and afterload, and also decreased DBP, which has the potential to compromise coronary perfusion pressure. Augmentation of central aortic SBP, as seen in aging and in the presence of hypertension and/or arterial disease, greatly increases cardiac work and pressure-related cardiac pathology, including both CAD and LV hypertrophy, because it is the pressure against which the LV must eject blood into the systemic circulation.

Oxidative Stress

Oxidative stress is a critical feature in both hypertension and atherogenesis.[17,18] Excessive generation of reactive oxygen species can damage endothelial or muscular cells and lead to acute and chronic changes in structure and function. For example, injured endothelium loses its vasodilator capacity and contributes to thrombosis and occlusion. Reactive oxygen species stimulate release of chemotactic cytokines and adhesion molecules on the luminal surface of the injured endothelium, thereby promoting adhesion of circulating leukocytes to the vessel wall. This low-grade, self-perpetuating vascular inflammatory process underlies the ongoing atherosclerotic process and contributes to continuing recruitment of leukocytes from the circulation into the subendothelial space. Inflammatory mediators also activate medial smooth muscle cells, causing them to proliferate and migrate into the subintimal space. In the presence of dyslipidemia, monocytes within the vessel wall incorporate oxidized low-density lipoprotein cholesterol and become lipid-laden macrophages, the core of the atherosclerotic plaque. In established lesions, resident macrophages secrete metalloproteinase and cathepsins, which may destabilize the fibrous cap of the plaque, result in plaque rupture, and release tissue factor to cause thrombosis, coronary occlusion, and acute myocardial infarction.

These processes may also contribute to the microcirculatory structural abnormalities seen in chronic hypertension. In vascular tissue, the principal effectors of oxidative injury are the NAD(P)H oxidases, which are activated by mechanical forces (eg, hypertension), hormones (particularly angiotensin II), oxidized cholesterol, and cytokines.[19] When cells are activated, these oxidases facilitate superoxide anion ($\cdot O_2^-$) generation. $\cdot O_2^-$ readily reacts with nitric oxide to form peroxynitrite ($ONOO^-$), a particularly toxic metabolite that also shortens the half-life of endothelium-derived nitric oxide. Reactive oxygen species such as hydrogen peroxide and $ONOO^-$ rapidly oxidize lipids, which makes them more atherogenic, and produce phenotypic changes such as vascular smooth muscle cell proliferation, adhesion molecule expression, and premature senescence in vascular cells.[20] Several NAD(P)H oxidase isoforms expressed in endothelial and vascular smooth muscle cells appear to be upregulated in the setting of atherosclerosis and arterial injury.[21]

Humoral and Metabolic Factors

Many of the mechanisms of the initiation and maintenance of hypertension are also those that mediate damage to target organs, including the coronary vessels and the myocardium. These mechanisms include increased sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) activity; deficiencies in release and/or activity of vasodilators, for example, nitric oxide, prostacyclin, and the natriuretic peptides; structural and functional abnormalities in conductance and resistance arteries, particularly endothelial dysfunction; and increased expression of growth factors and inflammatory cytokines in the arterial tree.[17] The corollary of this idea is that antihypertensive drugs may exert at least some of their beneficial effects on the vasculature by actions that are independent of BP lowering alone. This is controversial and will be discussed more fully in later sections.

Angiotensin II elevates BP and promotes target-organ damage, including atherosclerosis, by a large variety of mechanisms. There are direct effects of angiotensin II on constriction and remodeling of resistance vessels, aldosterone synthesis and release, enhancement of sympathetic outflow from the brain, and facilitation of catecholamine release from the adrenals and peripheral sympathetic nerve terminals.[18,22,23] Aldosterone may mimic or potentiate the vaso-

toxic properties of angiotensin II and norepinephrine.[24] Angiotensin II promotes cardiac and vascular smooth muscle cell hypertrophy directly via activation of the angiotensin II type 1 (AT1) receptor and indirectly by stimulating expression of a number of growth factors and cytokines, for example, platelet-derived growth factor, basic fibroblast growth factor, insulin-like growth factor-1, and transforming growth factor-β and their receptors, as well as monocyte chemoattractant protein-1 and vascular cell adhesion molecule-1. Finally, there is a link between RAAS activation and fibrinolysis. Angiotensin II induces the formation of plasminogen activator inhibitor-1 via an AT1 receptor–dependent effect on endothelial cells, whereas ACE downregulates tissue plasminogen activator production by degrading bradykinin, a potent stimulator of endothelial tissue plasminogen activator expression.[25,26]

ACE inhibitors and ARBs have been shown to limit oxidative reactions in the vasculature by blocking the activation of NAD(P)H oxidase, which supports the concept that these RAAS blockers may have important vasoprotective effects beyond BP lowering.[27] Furthermore, there is evidence of interaction between the RAAS and dyslipidemia, wherein hypercholesterolemia upregulates the RAAS, particularly vascular AT_1 receptor density and functional responsiveness, and systemic angiotensin II peptide synthesis,[28,29] whereas the RAAS stimulates the accumulation of low-density lipoprotein cholesterol in the arterial wall.[30]

Calcium

Calcium ions (Ca^{2+}) are major intracellular mediators of vascular smooth muscle cell contraction, as well as of inotropic and chronotropic functions of the heart. Ca^{2+} enters vascular smooth muscle cells, cardiomyocytes, and pacemaker cells via voltage-dependent L- and T-type calcium channels.[31] In vascular smooth muscle, the voltage-gated L-type (long-acting, slowly activating) channel allows entry of sufficient Ca^{2+} for initiation of contraction by calcium-induced intracellular Ca^{2+} release from the sarcoplasmic reticulum. In addition to these acute regulatory functions, increased intracellular Ca^{2+} has atherosclerosis-promoting effects.[32]

The dihydropyridine calcium channel blockers (CCBs) bind to a common site on the α_1-subunit of the L-type channel. The dihydropyridine CCBs are highly selective for arterial/arteriolar tissues, including the coronary arteries, where they cause vasodilation. The nondihydropyridine CCBs, including the phenylalkylamines (verapamil-like) and benzothiazepines (diltiazem-like), bind to different sites on the α_1-subunit and are less selective for vascular smooth muscle; they have negative chronotropic and dromotropic effects on sinoatrial and atrioventricular nodal conducting tissue and negative inotropic effects on cardiomyocytes. The nondihydropyridine CCBs have greater effects on the atrioventricular node than on the sinoatrial node and may predispose to high-degree atrioventricular block when administered to patients with preexisting atrioventricular nodal disease or when given with other agents, for example, β-blockers, that depress the atrioventricular node. Both dihydropyridine CCBs and nondihydropyridine CCBs are indicated for the treatment of hypertension and angina pectoris. The antianginal effects of CCBs result from afterload reduction, that is, their ability to decrease SBP, as well as coronary vasodilation, and in the case of nondihydropyridine CCBs, heart rate slowing. CCBs are particularly effective in treating angina due to coronary spasm, for example, Prinzmetal's variant or cold-induced angina.[33]

Primary Prevention of CAD in Hypertension

Primary Versus Secondary Prevention

IHD can be prevented or reversed when aggressive targets are achieved for major cardiovascular disease risk factors.[2,34] The distinction between primary and secondary prevention is arbitrary, because the major therapeutic objective in any individual is to retard or reverse the underlying atherosclerotic disease process. Furthermore, existing therapies are the same for primary or secondary cardiac protection. The effectiveness of any therapy is judged by the degree of reduction in the surrogate end point (BP) and the ability of the chosen regimen to reduce clinical end points (eg, myocardial infarction [MI]).

BP and Treatment Goals

The overall goal of therapy is to reduce excess morbidity and unnecessary deaths. In the case of hypertension, dyslipidemia, and diabetes mellitus, surrogate end points (BP, cholesterol, and blood glucose) have been established as diagnostic markers, and discrete values of these markers have been established as therapeutic targets. The current consensus target for BP is $<$140/90 mm Hg in general and $<$130/80 mm Hg in individuals with diabetes mellitus or chronic kidney disease.[2,13,14] Recently, it has been found that treatment of prehypertension (BP 120 to 139/80 to 89 mm Hg) reduces the incidence of subsequent hypertension.[11] An analysis of the 274 patients with CAD who completed the intravascular ultrasound substudy of the CAMELOT (Comparison of AMlodipine versus Enalapril to Limit Occurrences of Thrombosis) trial[35] showed that those subjects with a "normal" BP according to the definition given in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[2] ($<$120/80 mm Hg) had a mean decrease of atheroma volume of 4.6 mm^3; "prehypertensive" (120 to 139/80 to 89 mm Hg) subjects had no significant change; and "hypertensive" ($\geq$140/90 mm Hg) subjects had a mean increase in atheroma volume of 12.0 mm^3. There is, therefore, a very powerful historical trend for lower BP goals, especially in those with target-organ damage. There remains, however, controversy about specific BP treatment goals for individuals with nascent or overt CAD. On the one hand, it can be argued from pathophysiological principles that very low SBP values (ie, $<$120 mm Hg) may be appropriate to reduce myocardial workload.[2,36] At the same time, there is a concern that excessive lowering of DBP may impair coronary perfusion.

At present, there are no clinical trials specifically designed to answer the question of what the most appropriate BP target(s) should be in individuals with latent or overt CAD. Judgments and recommendations must be based on the analysis of large epidemiological studies, such as the data in

986 000 individuals followed up for a median of 12.7 years in the Prospective Studies Collaboration, in which there was a strong log-linear association between BP and cardiovascular disease risk. Over the range of 115/75 to 185/115 mm Hg, each 20-mm Hg elevation in SBP (or 10-mm Hg elevation in DBP) roughly doubled the risk of dying of IHD or stroke.[5] Although epidemiological correlations cannot be used as proof of the value of treatment, they are useful in establishing expectations for reasonable treatment strategies. However, on the basis of this huge cohort and prospective studies such as the intravascular ultrasound substudy of CAMELOT,[35] it appears reasonable to propose that the target BP for individuals at risk for the development of CAD should be lower than that for low-risk individuals. Specifically, we recommend a target BP of <130/80 mm Hg for individuals with demonstrated CAD, or CAD risk equivalents (carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm), and for high-risk patients, defined as those with diabetes mellitus, chronic renal disease, or a 10-year Framingham risk score of ≥10%.

We believe that the Framingham risk score together with the presence or absence of diabetes mellitus or chronic renal disease effectively predicts CAD risk, at least in a middle-aged white population. The Framingham risk score is a simple prediction algorithm that uses categorical variables; it was also used as the basis of risk stratification in the Adult Treatment Panel III guidelines of the National Cholesterol Education Program to establish guidelines for the treatment of dyslipidemias.[15] Strong support for the use of a simple risk score such as the Framingham risk score has been provided very recently from the Framingham Heart Study in an investigation of the possible incremental usefulness of multiple biomarkers for predicting the risk of cardiovascular events. The finding was that the use of 10 "contemporary" biomarkers, namely, high-sensitivity C-reactive protein, brain natriuretic peptide, N-terminal pro-atrial natriuretic peptide, aldosterone, renin, fibrinogen, plasminogen activator inhibitor-1, D-dimer, homocysteine, and albuminuria, added very little to the overall prediction of risk based on the conventional cardiovascular risk factors of age, cigarette smoking, BP, total and high-density lipoprotein cholesterol, and presence or absence of diabetes mellitus.[37]

Coronary Perfusion and the J Curve

Many studies demonstrate that lowering either SBP or DBP decreases overall cardiovascular risk. Yet, concern has persisted that excessive DBP lowering may have adverse consequences for the heart. In virtually all instances, lowering SBP improves cardiac function and outcomes, probably through reduction in cardiac work and improved myocardial oxygen balance. On the other hand, it is theoretically possible that lowering of DBP improves cardiovascular outcomes only when coronary perfusion is maintained above the lower limit of coronary autoregulation.

Coronary Autoregulation

Myocardial perfusion occurs almost exclusively during diastole, and therefore DBP is the coronary perfusion pressure. Like most vascular beds, the coronary circulation is capable of autoregulation, such that a fall in perfusion pressure is accompanied by coronary vasodilation, which maintains a fairly constant coronary blood flow. The problem is that this ability of coronary resistance vessels to dilate in response to a falling perfusion pressure is limited, and at the point of maximal vasodilation, a further fall in coronary perfusion pressure will result in a decrease in flow. In conscious instrumented dogs, contractile function (transmural wall thickening and subendocardial segment shortening) is well maintained at mean coronary filling pressures down to 40 mm Hg, which corresponds to a DBP of ≈30 mm Hg.[38] The lower limit of autoregulation in dogs with LV hypertrophy is shifted upward by ≈15 to 20 mm Hg but can be partially restored by ACE inhibition, with accompanying regression of LV hypertrophy.[39] These studies were in dogs with normal intramural coronary arteries. We do not have good data on equivalent values for the human coronary circulation.

In the presence of occlusive coronary disease, the hemodynamics become much more complicated. Significant CAD will shift the lower autoregulatory limit upward. However, because myocardial blood flow is very heterogeneous,[40] the consequences of coronary underperfusion are unpredictable and may depend on the intramyocardial wall stress (which in turn is increased by a high arterial pressure but decreased by LV hypertrophy), the effects of antihypertensive medications on these variables, and, of course, the severity of the occlusive coronary disease.

There is also a lowered coronary flow reserve (defined as the difference between resting flow and flow through a maximally dilated coronary circulation, at any level of perfusion pressure) in patients with LV hypertrophy or with coronary atherosclerosis and/or microangiopathy, with a reduced functional or structural capacity of coronary resistance vessels to dilate.[41] This potential for impairment of myocardial oxygen supply may be compounded by an increased myocardial oxygen demand due to exercise, LV hypertrophy (if present), and the increase in the output impedance of the LV because of the increased SBP. This combination of a lowered oxygen supply and an increased oxygen demand, especially during exercise, is particularly pernicious in the heart, because the heart is an aerobic organ that can develop only a small oxygen debt, and oxygen extraction is almost maximal even at rest and can increase little with increased demand.

It is theoretically possible, therefore, that although lowering BP improves cardiovascular outcomes in hypertensive patients as long as coronary perfusion is maintained above the lower autoregulatory limit for coronary blood flow, any further reduction of DBP to levels below the lower autoregulatory limit could reduce coronary blood flow, especially when myocardial oxygen consumption is increased, such as during exercise, and that this could be translated to an upturn in the incidence of coronary events as DBP is lowered beyond this point. The relationship between DBP and coronary events would, if this were true, show a J-shaped curve. A major difficulty is that we do not have data about the DBP level that corresponds to the lower limit of autoregulation in the intact human coronary circulation, and even fewer data in patients

with hypertension and CAD. It would be reasonable to assume, also, that a rapid reduction in DBP to very low levels may be more hazardous in patients with combined hypertension and CAD, although we have no experimental or clinical trial evidence to support this idea. We therefore must rely on observational studies and clinical trials data to resolve this issue.

Observational Studies

If coronary autoregulation is clinically important, it would be predicted that a U-shaped or J-shaped relationship should exist between DBP and CAD events. It would also be logical to assume that an unduly rapid decrease in coronary perfusion pressure could precipitate a coronary event, whereas more gradual lowering of coronary perfusion pressure may allow appropriate physiological or structural adaptations to occur. There is epidemiological evidence to both support and refute the existence of a J curve. The first retrospective study in 1979 reported a 5-fold increase in MI among treated patients with DBP (Korotkoff phase IV) values of <90 mm Hg (Korotkoff phase V, ≈80 to 85 mm Hg).[42] This observation was confirmed by a subsequent meta-analysis in 1987[43] and by more recent reanalysis of the 1985 Medical Research Council's trial of mild hypertension, which reported an increased MI prevalence in those with achieved DBP of <80 mm Hg.[44] In these analyses, investigators using the same data have drawn opposite conclusions about whether a J curve really exists.[45,46] There is much debate and disagreement regarding methodological assumptions and pitfalls, and several reports have articulated how confounding variables, especially age and comorbidities, including late-stage HF, could have affected the conclusions.[47–50]

In none of the retrospective analyses was it possible to control adequately for the many interacting comorbid conditions that accompany and confound low DBP or for the complex relationships among age, DBP, and cardiovascular disease risk. Age, DBP, and cardiovascular risk are positively associated until about age 50 years. For the remainder of life, DBP decreases and pulse pressure widens, whereas cardiovascular risk increases logarithmically. Age is by far the most important risk factor for CAD; the prevalence of fatal ischemic cardiac events increases by 64-fold as age doubles from 40 to 80 years. Yet a high SBP, a low DBP, and a wide pulse pressure are each independent risk factors for CAD.[51,52] Thus, the effects of aging cannot be separated easily from those of low DBP or wide pulse pressure in predicting the risk of a fatal MI, primarily because the exponent of the age-cardiovascular disease risk relationship is greater and more consistent than the impact of the (curvilinear) relationship between either age and diastolic DBP or diastolic DBP and cardiovascular disease risk. This important confounder is sufficient to explain much of the confusion over the existence of a J curve in observational studies. In the Framingham Heart Study, after 12 years of follow-up of ≈7800 participants initially free of cardiovascular disease, a statistically significant excess of cardiovascular events was found in those with isolated systolic hypertension (follow-up pressures >140 systolic and <80 mm Hg diastolic).[51] These results suggest that wide pulse pressure is a significant determinant of whether high diastolic DBP is a major risk predictor. In fact, another reanalysis of the Framingham data demonstrates that DBP is useful as a cardiovascular disease risk predictor only in individuals younger than age 50 years, whereas SBP elevation is most important in older individuals.[4]

Perhaps the strongest evidence that a treatment-induced fall in DBP does not increase cardiovascular risk is a meta-analysis of individual patient data from 7 randomized clinical trials.[52] A J-shaped relationship was observed between DBP and mortality in both treated and untreated hypertensive subjects. There was also a J curve for noncardiovascular mortality in the treated group (but not in the untreated subjects). The conclusion was that increased risk in patients with low BP was not primarily related to antihypertensive treatment or BP-related events but more likely to poor health conditions that caused a low BP.

Clinical Trials

Data from controlled trials have not shown a J curve. In the Hypertension Optimal Treatment (HOT) trial, ≈19 000 patients with average pretreatment BPs of 170/105 mm Hg were randomized to 3 treatment groups with different DBP targets, namely, ≤90, ≤85, or ≤80 mm Hg.[53] At the end of the study, there was little separation in the achieved DBP (mean values 85.2, 83.2, and 81.1 mm Hg, respectively), which impaired the power to detect any meaningful difference among treatment groups. Lower BPs did not further decrease or increase the incidence of adverse cardiovascular events, except for a small increase in mortality in those whose diastolic pressures were reduced to <70 mm Hg.[53,54] Of note, the diabetic subgroup of HOT clearly benefited when DBP was <80 mm Hg.

In the International Verapamil-Trandolapril Study (INVEST) of ≈22 000 patients with known CAD and hypertension, DBP values lower than 70 mm Hg were associated with increased risk for MI[55]; however, subjects with DBP <70 mm Hg were older than those with higher DBP and were more likely to have a history of MI, bypass surgery and angioplasty, diabetes mellitus, HF, and cancer. In the Irbesartan Diabetic Nephropathy Trial (IDNT) of ≈1600 patients with hypertension and diabetic nephropathy, the incidence of MI was increased in those with DBP values <80 mm Hg, with a 61% increase in the relative risk per each 10-mm Hg decrease in diastolic DBP.[56] In that study, the inverse relationship between DBP and relative risk of MI extended over the entire range of diastolic pressures from 95 mm Hg to 55 mm Hg. This is inconsistent with the data from nearly all of the early trials of antihypertensive therapy, which showed a clear cardioprotective effect of lowering DBP. In the CAMELOT trial,[57] 60% of 1991 patients had hypertension and angiographically documented CAD. Most were already being treated with a β-blocker, one third were taking a diuretic, and the mean entry BP was 129/77 mm Hg. Treatment with either an ACE inhibitor or a CCB lowered BP by an additional 5/2 mm Hg, with no evidence of a J curve in either treated group.

Conclusions

Although lower SBP values are associated with better IHD outcomes, the evidence that excessive lowering of DBP may compromise cardiac outcomes (the J curve) is inconsistent.

Epidemiological and clinical trial evidence both supports and refutes the existence of a J curve for DBP but not SBP, which suggests the presence of major confounders of data interpretation, including selection bias, comorbidities, and nonlinear interactions among age, decreasing DBP, and increasing cardiovascular risk. The vast majority of hypertensive individuals, including those with wide pulse pressures or overt cardiac disease, will not experience problems related to lowering of DBP when standard antihypertensive medications are used. Concerns that coronary perfusion is limited by an autoregulatory threshold have not yet been validated in humans with healthy or diseased coronary arteries, and no consensus exists regarding the minimum safe level of DBP in these individuals.[58] Nevertheless, in view of the uncertainty on this issue, it would seem prudent to counsel that in patients with an elevated DBP and occlusive CAD with evidence of myocardial ischemia, the BP should be lowered slowly, and caution is advised in inducing falls of DBP below 60 mm Hg if the patient has diabetes mellitus or is over the age of 60 years. In older hypertensive individuals with wide pulse pressures, lowering SBP may cause very low DBP values (<60 mm Hg). This should alert the clinician to assess carefully any untoward signs or symptoms, especially those due to myocardial ischemia.

Nonpharmacological Therapies

Although hypertension, hypercholesterolemia, cigarette smoking, obesity, and sedentary lifestyles are potentially modifiable risk factors for IHD,[2,12] it has never been proven that lifestyle modifications can reduce clinical events in individual patients. Nevertheless, recommendations for modification of these risk factors are appropriate for reducing the burden of hypertension in the population as a whole. Tightly controlled dietary modification, as in the Dietary Approaches to Stop Hypertension (DASH) study,[59] can reduce mean SBP by a modest amount: 3.0, 6.2, and 6.8 mm Hg in subjects on a low-, intermediate-, and high-sodium intake diet, respectively. In the DASH study, all food was provided. Secondary protection has been claimed for aggressive calorie-restricted and low-fat diets, which in a small study[60] reduced the recurrence of acute MI, but the feasibility of stringent dietary modification in the general population has not been clearly established. Nevertheless, lifestyle modifications, including smoking cessation, weight loss, reduced sodium intake, moderation of alcohol consumption (among those who drink), exercise, and an overall healthy dietary pattern,[61,62] are entirely appropriate for patients with CAD.

Pharmacological Therapy

The most important strategy for lowering the burden of atherosclerotic disease is fastidious BP control. Although it might be anticipated that some classes of antihypertensive drugs, through mechanisms independent of their BP-lowering action, may have greater antiatherosclerotic actions than others, this has not been demonstrated convincingly. Meta-analyses have demonstrated that BP lowering is more important than choice of drug class in the primary prevention of the complications of hypertension.[63,64] Furthermore, effective combination antihypertensive drug therapy is usually required to achieve and sustain effective long-term BP control.[2] Thus, the question of which class of agents to use first in hypertension is essentially moot.

In contrast, for secondary protection in individuals with "compelling indications" such as IHD, chronic kidney disease, or recurrent stroke, not all drug classes have been proven to confer optimal benefit. Patients who have had an MI or who have HF have improved outcomes with ACE inhibitor therapy, consistent with the actions of these drugs in preventing or retarding atherogenesis.[65] However, both the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial[66] and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[67] failed to show any particular benefit for valsartan and lisinopril, respectively, over comparator drugs of other classes. There is also continuing debate over whether there are "class effects" for antihypertensive drugs or whether each drug must be considered individually. It is reasonable to assume that there are class effects for thiazide-type diuretics, ACE inhibitors, and ARBs, which have a high degree of homogeneity in their mechanisms of action and side effects. It is equally clear that there are major differences between drugs within more heterogeneous classes of agents, such as β-blockers or CCBs.

Thiazide-Type Diuretics

Thiazides are highly effective in reducing BP and preventing cerebrovascular events, as demonstrated most convincingly in early studies such as the Veterans Administration studies,[68] the Medical Research Council (MRC) trial,[69] and the Systolic Hypertension in the Elderly Program (SHEP).[70] The benefit of thiazide-based therapy in hypertension treatment is evident from the large ALLHAT trial.[67] In the aftermath of ALLHAT, there are continuing concerns about whether thiazide-induced hyperglycemia and diabetes mellitus contribute to long-term IHD risk not measured during the study interval.[71]

β-Blockers

β-Blockers comprise a relatively heterogeneous class of antihypertensive drugs with differing effects on resistance vessels and on cardiac conduction and contractility. β-Blocker administration remains a standard of care in patients with angina pectoris, those who have had an MI, and those who have LV dysfunction with or without HF symptoms, unless contraindicated.[63] The β-blockers carvedilol, metoprolol, and bisoprolol have been shown to improve outcomes in patients with HF. However, in patients who do not have symptomatic CAD, have not had an MI, or do not have HF, the evidence for β-blocker cardioprotection is weak, especially in the elderly,[72] and there are other studies that suggest a relative lack of benefit on cerebrovascular[73] and renal[74] disease end points. In the Controlled-ONset Verapamil IN Cardiovascular Endpoints (CONVINCE) trial[75] and the INVEST study,[55] outcomes with verapamil-based therapy were similar to those with β-blocker–based therapy. The large Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) was stopped prematurely because atenolol-based therapy was inferior to amlodipine-based therapy in reducing cardiovascular events,[76] and in the Conduit Artery Function Evaluation (CAFÉ) substudy of ASCOT, atenolol was found to be less effective than amlo-

dipine in reducing central SBP and cardiac afterload, which perhaps explains the lesser benefits of β-blockers.[77]

ACE Inhibitors

ACE inhibitors, a relatively homogeneous class of antihypertensive agents, are effective in reducing initial IHD events and are recommended for consideration in all patients after MI. They are proven to forestall and treat HF[78,79] and kidney failure,[80] and when combined with thiazide-type diuretics, they also reduce the incidence of recurrent stroke.[81]

Three major trials have addressed the use of ACE inhibitors in patients with or at high risk for CAD but without HF or known significant LV systolic impairment. In HOPE, 9297 patients 55 years of age or older who had evidence of vascular disease or diabetes mellitus plus 1 other cardiovascular risk factor were assigned to receive either ramipril (target dose 10 mg/d) or placebo and followed up for a mean of 5.0 years.[82] Forty-seven percent of patients were hypertensive, and 8.4% had electrocardiographic evidence of LV hypertrophy. Treatment with ramipril was associated with a 22% reduction in the composite end point of cardiovascular death, MI, and stroke ($P<0.001$) and comparably significant reductions in each of the individual components. The magnitude of the reduction in the composite end point was similar for patients with and without hypertension at baseline. There were also significant reductions in the rates of revascularization, cardiac arrest, HF, worsening angina, and all-cause mortality with ramipril therapy. The mean reduction in BP with active treatment was small (3/2 mm Hg). These cardiovascular benefits were initially claimed to be independent of BP, but an important HOPE substudy revealed a marked reduction in 24-hour ambulatory BP with the ACE inhibitor that was missed in the main trial that measured only office BPs.[83]

The EUROPA investigators randomized 12 218 patients to perindopril or placebo.[84] Only 27% of patients were classified as hypertensive, although the definition was based on a BP recording in excess of 160/95 mm Hg or treatment with antihypertensive medications at baseline. Mean follow-up was 4.2 years. Perindopril therapy (target dose 8 mg/d) was associated with a 20% relative risk reduction in the primary end point, a composite of cardiovascular death, MI, or cardiac arrest ($P=0.003$). The benefit of active treatment with perindopril was similar for patients with or without hypertension. The mean reduction in BP was 5/2 mm Hg. EUROPA patients were at lower risk than HOPE patients; one third were younger than 55 years, fewer had diabetes mellitus (12% versus 39%), and proportionately more EUROPA patients used antiplatelet (92% versus 76%) and lipid-lowering (58% versus 29%) drugs.

In an even lower-risk group than the subjects in EUROPA, patients in the Prevention of Events with Angiotensin Converting Enzyme inhibition (PEACE) trial had stable CAD and normal or slightly reduced LV function and were randomized to trandolapril (target dose 4 mg) or placebo.[85] Median follow-up was 4.8 years. No difference between the groups was found in the incidence of the primary composite end point of cardiovascular death, MI, or coronary revascularization. Forty-six percent of patients were hypertensive, and treatment with trandolapril was associated with a mean 4.4/3.6-mm Hg reduction in BP. The annualized rate of all-cause mortality was only 1.6%, a rate similar to that of an age- and sex-matched cohort without CAD. The investigators concluded that ACE inhibitors might not be necessary as routine therapy in low-risk CAD patients with preserved LV function, especially those who have received intensive treatment with revascularization and lipid-lowering agents.

Thus, 2 large studies (HOPE and EUROPA) showed cardioprotection by ACE inhibitors, and 1 (PEACE) did not. In addition, cardiovascular protection with captopril was demonstrated in the SAVE trial.[86] However, in ALLHAT, there were no significant differences between the thiazide diuretic chlorthalidone, the calcium antagonist amlodipine, and the ACE inhibitor lisinopril in the combined outcomes of fatal CAD and nonfatal MI (the primary outcome of the study), in combined CAD (the primary outcome plus coronary revascularization or hospitalization for angina), or in all-cause mortality.[67] Soon after the ALLHAT results were published, the Second Australian National Blood Pressure Study Group (ANBP-2) reported the results of a prospective, open-label study in patients 65 to 84 years of age who had hypertension that showed, in men but not in women, better cardiovascular outcomes with ACE inhibitors than with diuretics despite similar reductions in BP.[87]

Angiotensin Receptor Blockers

ARBs are highly uniform in their cardiovascular effects, and several have been shown to reduce the incidence or severity of IHD events, renal failure, and cerebrovascular events. ARBs are generally considered to be appropriate therapy in individuals with cardiovascular disease who are intolerant of ACE inhibitors. Primary protection against cardiovascular events similar to that produced by a calcium antagonist (amlodipine) was demonstrated in the VALUE study.[65] Positive cardiovascular disease outcomes were not found in the OPtimal Trial In Myocardial infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL),[88] but these negative results were most likely due to inadequate doses. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), ARB therapy was similar to ACE inhibition in reducing cardiovascular event end points.[89] However, in VALIANT, the addition of the ARB to adequate doses of an ACE inhibitor yielded an increase in adverse events with no incremental benefit for cardiovascular events.

Aldosterone Antagonists

As add-on to conventional antifailure therapy, spironolactone and eplerenone lowered BP and had a secondary protective effect in patients with severe HF in the Randomized Aldactone Evaluation Study (RALES)[90] and in patients with LV dysfunction after MI in the Eplerenone Post-acute myocardial infarction HEart failure efficacy and SUrvival Study (EPHESUS) trial.[91] There has been no major study of cardiovascular outcomes in individuals treated with aldosterone antagonists for hypertension without LV dysfunction.

Calcium Channel Blockers

L-channel CCBs form a heterogeneous class of agents with similar BP effects but differing actions on cardiac conduction and contractility. Primary prevention of cardiovascular events

with the dihydropyridine CCB amlodipine was equivalent to that produced by thiazide diuretic or ACE inhibitor–based therapy in ALLHAT,[67] and superiority over a β-blocker was claimed in ASCOT.[76] Primary protection with verapamil-based therapy was shown to be similar to diuretic- or β-blocker–based therapy in CONVINCE[75] and INVEST.[55] In the NORdic DILtiazem (NORDIL) study, overall cardiovascular event rates were similar for diltiazem and a combination of diuretic and β-blocker.[92] Calcium antagonists are alternatives to β-blockers in the treatment of angina but are not generally recommended for secondary cardiac protection because of the relative inability of this class to prevent ventricular dilatation and HF,[93] especially compared with ACE inhibitors[67] or ARBs.[66]

Limitations of Clinical Trials

All clinical trials are inherently limited by a number of important methodological problems. The most common confounder is the heterogeneity of the populations included in the study. In many studies, results are driven by particular subpopulations, and the main trends reported may not extend to the population at large. In most trials, multiple drugs are used, and the reported outcomes are the result of the interaction of several agents. Another pitfall in many clinical trials is the failure to investigate higher doses of drugs. Accordingly, there is a strong tendency to find that combination or add-on therapies are more effective than single agents; however, uptitration of the background therapy might have been equally efficacious. This is especially problematic for drugs that have overlapping mechanisms of action (such as agents that inhibit components of the RAAS, for example, β-blockers, ACE inhibitors, ARBs, and aldosterone antagonists). These important caveats limit the applicability of trial results to everyday practice and make physician judgment a major factor in choosing optimal therapy for individual patients.

Recommendations

1. **For the primary prevention of CAD in hypertension, aggressive BP lowering is appropriate, with a target BP of <130/80 mm Hg in individuals with any of the following: diabetes mellitus; chronic renal disease; CAD; CAD risk equivalents; carotid artery disease (carotid bruit, or abnormal carotid ultrasound or angiography); peripheral arterial disease; abdominal aortic aneurysm; and for high-risk patients, defined as those with a 10-year Framingham risk score of ≥10% (see Appendix); and a target BP of <140/90 mm Hg in individuals with none of the above *(Class IIa; Level of Evidence B)*.**
2. **In patients with an elevated DBP and CAD with evidence of myocardial ischemia, the BP should be lowered slowly, and caution is advised in inducing falls of DBP below 60 mm Hg if the patient has diabetes mellitus or is over the age of 60 years. In older hypertensive individuals with wide pulse pressures, lowering SBP may cause very low DBP values (<60 mm Hg). This should alert the clinician to assess carefully any untoward signs or symptoms, especially those due to myocardial ischemia. In the very old, those over 80 years of age, antihypertensive therapy is effective in reducing stroke risk, but evidence for a reduction in coronary events is less certain *(Class IIa; Level of Evidence C)*.**
3. **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 cardiovascular 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 mm Hg above goal, 2 drugs should usually be used from the outset. In the asymptomatic post-MI patient, a β-blocker is a more appropriate choice for secondary prevention for at least 6 months after the infarction and is the drug of first choice if the patient has angina pectoris. This is discussed further in the next section *(Class I; Level of Evidence A)*.**

Management of Hypertension in Patients With CAD and Stable Angina

Management of hypertension in patients with chronic CAD and chronic stable angina is directed toward the prevention of death, MI, and stroke; a reduction in the frequency and duration of myocardial ischemia; and the amelioration of symptoms. Lifestyle changes and the adoption of a heart-healthy approach are critical, with the usual attention to diet, sodium intake, moderation of alcohol, regular exercise, weight loss, smoking cessation, glycemic control, lipid management, and antiplatelet therapy. Recognition and treatment of hypothyroidism and obstructive sleep apnea are important adjuncts in at-risk patients. Pharmacological management is inevitably required. A reasonable BP target for hypertensive patients with demonstrated CAD or with CAD risk equivalents (carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm, diabetes mellitus, or chronic renal disease) is <130/80 mm Hg, as described in the previous section.

Pharmacological Therapy

β-Blockers

β-Blockers are the drugs of first choice for the treatment of hypertension in patients with CAD that causes angina.[94] They alleviate ischemia and angina primarily as a function of their negative inotropic and chronotropic actions. The decreased heart rate increases diastolic filling time for coronary perfusion. β-Blockers also inhibit renin release from the juxtaglomerular apparatus. Cardioselective (β1) agents without intrinsic sympathomimetic activity are used most frequently. Relative contraindications to their use include significant sinus or atrioventricular node dysfunction, hypotension, decompensated HF, and severe bronchospastic lung disease. Peripheral arterial disease is rarely made symptomatically

worse by the use of these agents, and mild bronchospastic disease is not an absolute contraindication. Caution is needed when treating brittle diabetic patients with a history of hypoglycemic events, because β-blockers may mask the symptoms of hypoglycemia. Recently, there has been considerable controversy concerning the appropriateness of using β-blockers as first-line therapy in hypertension in those patients who do not have a compelling indication; however, their use in patients with angina, prior MI, or HF has a solid basis of positive data. The use of β-blockers for secondary prevention in all but the lowest-risk patients is a Class I American College of Cardiology (ACC)/AHA recommendation (**Level of Evidence A**).[95] Even for the lowest-risk patients, the weight of evidence and consensus opinion favor their use (**Class IIa ACC/AHA recommendation, Level of Evidence B**).[95]

Calcium Channel Blockers

CCBs are added to, or substituted for, β-blockers when BP remains elevated, when angina persists, or when drug side effects or contraindications mandate.[96] As a class, CCBs reduce myocardial oxygen demand by decreasing peripheral vascular resistance and lowering BP and increase myocardial oxygen supply by coronary vasodilation. The nondihydropyridine agents, diltiazem and verapamil, also decrease the sinus node discharge rate and slow atrioventricular nodal conduction. Long-acting dihydropyridine agents are preferred over nondihydropyridines for use in combination with β-adrenoreceptor blockers, to avoid excessive bradycardia or heart block. Diltiazem or verapamil should not be used in patients with HF or LV systolic dysfunction,[97] and short-acting nifedipine should be avoided because it causes reflex sympathetic activation and worsening myocardial ischemia.[94]

Although CCBs are useful in the management of angina, there is no consensus about their role in preventing cardiovascular events in patients with established CAD. The INVEST investigators randomized >22 000 hypertensive patients with chronic CAD to the nondihydropyridine CCB verapamil or the β-blocker atenolol.[55] By 24 months, the ACE inhibitor trandolapril had to be added in 63% of verapamil patients and 52% of atenolol patients, and hydrochlorothiazide was added in 44% of verapamil and 60% of atenolol patients, respectively. There was no difference between the groups in the composite end point of death, MI, or stroke over a mean follow-up of 2.7 years. More than 50% of patients in ALLHAT had a history or signs of atherosclerotic vascular disease, and there was no significant difference in the incidence of coronary end points among patients allocated a thiazide diuretic, a long-acting dihydropyridine CCB, or an ACE inhibitor.[67] CAMELOT compared amlodipine or enalapril to placebo in normotensive patients with CAD, ≈60% of whom had a history of hypertension.[57] Although BP reduction was similar in the 2 active treatment groups, adverse cardiovascular events occurred less frequently in the amlodipine group than in the enalapril group. An intravascular ultrasound substudy showed progression of atherosclerosis in the placebo group ($P<0.001$), a trend toward progression in the enalapril group ($P=0.08$), and no progression in the amlodipine group ($P=0.31$). Amlodipine may have pleiotropic effects beyond BP lowering that favor atherosclerotic plaque stabilization.[98]

The VALUE trial randomized 15 245 hypertensive patients at high risk of cardiac events to valsartan or amlodipine.[66] Forty-six percent of patients in both groups had CAD. Mean follow-up was 4.2 years. No difference between groups was observed in the primary composite end point of cardiac morbidity and mortality. The risk of MI was lower in the amlodipine group, whereas the risk of new-onset diabetes mellitus was lower in the valsartan group. Of note, amlodipine was significantly more effective in reducing BP, especially over the first year of the trial. There was also a strong trend for an excess risk of stroke in the valsartan group, likely due to this same BP differential that favored amlodipine. The investigators highlighted the need for aggressive BP control in high-risk hypertensive patients, a goal that frequently requires combination therapy at the outset, a concept supported by the Blood Pressure Lowering Treatment Trialists' Collaboration.[99]

ACE Inhibitors

The long-term use of ACE inhibitors in patients with CAD who also have diabetes mellitus and/or LV systolic dysfunction is a Class I ACC/AHA recommendation (**Level of Evidence A**).[94,95,97] Their use is also particularly appropriate for CAD patients with hypertension. The clinical trials that support the use of ACE inhibitors in the management of patients with stable CAD were described in the last section. They are the HOPE study,[82] in which high-risk individuals given an ACE inhibitor (ramipril 10 mg/d) experienced a reduction in cardiovascular disease end points by 20% to 25%; EUROPA,[84] which showed a 20% relative risk reduction in the primary end point, a composite of cardiovascular death, MI, or cardiac arrest in patents treated with perindopril 8 mg/d versus placebo; and SAVE.[86]

On the other hand, there have been negative studies, also described in the previous section. These include PEACE,[85] in which patients with stable CAD and normal or slightly reduced LV function were randomized to trandolapril (target dose 4 mg) or placebo. No difference between the groups was found in the incidence of the primary composite end point of cardiovascular death, MI, or coronary revascularization. In ALLHAT,[67] there were no significant differences among chlorthalidone, amlodipine, and lisinopril in the combined outcomes of fatal CAD and nonfatal MI (the primary outcome of the study), in combined CAD (the primary outcome plus coronary revascularization or hospitalization for angina), or all-cause mortality. It has already been noted that soon after the ALLHAT results were published, ANBP-2 reported the results of a prospective, open-label study in patients aged 65 to 84 years with hypertension that showed, in men but not in women, better cardiovascular outcomes with ACE inhibitors than with diuretic agents despite similar reductions in BP.[87]

Angiotensin Receptor Blockers

ARBs are indicated during hospitalization and at discharge for STEMI patients who are intolerant of ACE inhibitors and have HF or an ejection fraction <0.40 (**Class I ACC/AHA recommendation, Level of Evidence B**).[95] The combination

of ACE inhibitors and ARBs has been used for the treatment of advanced or persistent HF in the convalescent or chronic phase after STEMI (**Class IIb ACC/AHA recommendation, Level of Evidence B**).[97]

In the VALUE trial,[66] there was no difference in cardiac mortality and morbidity in patients with hypertension and high risk of cardiovascular events who were treated with regimens based on valsartan versus amlodipine, even though the BP-lowering effect of amlodipine was greater than that of valsartan. In VALIANT,[89] valsartan was as effective as captopril in patients who were at high risk for cardiovascular events after MI.

Diuretics

Thiazide diuretics reduce cardiovascular events, as demonstrated most convincingly in early studies, such as the Veterans Administration studies,[67] the MRC Trial,[69] and SHEP,[69] and in later studies, such as ALLHAT.[67] These studies are discussed in greater detail in the previous section.

Nitrates

Long-acting nitrates are indicated for the treatment of angina not controlled with adequate doses of β-blockers and CCBs in hypertensive CAD patients. Nitrates are also used in combination with hydralazine in selected HF patients, with or without hypertension.[97] They should not be used with phosphodiesterase inhibitors of the sildenafil type. Hypertension does not impact the use of long-acting nitrates for the prevention of angina or of sublingual nitrate preparations for relief of an anginal attack. Conversely, nitrates have not been shown to be of use in the management of hypertension.

Recommendations

The management of symptomatic CAD, particularly angina pectoris, is directed to the relief of the angina and the prevention of both the progression of CAD and coronary events. The mainstays of angina treatment are β-blockers, CCBs, and nitrates. Pharmacological strategies for the prevention of cardiovascular events in these patients include ACE inhibitors, ARBs, thiazide diuretics, β-blockers (particularly after MI), CCBs, antiplatelet drugs, and drugs for the treatment of dyslipidemia.

1. **Patients with hypertension and chronic stable angina should be treated with a regimen that includes a β-blocker in patients with a history of prior MI, an ACE inhibitor or ARB if there is diabetes mellitus and/or LV systolic dysfunction, and a thiazide diuretic *(Class I; Level of Evidence A)*. The combination of a β-blocker, ACE inhibitor or ARB, and a thiazide diuretic should also be considered in the absence of a prior MI, diabetes mellitus, or LV systolic dysfunction *(Class IIa; Level of Evidence B)*.**
2. **If β-blockers are contraindicated or produce intolerable side effects, a nondihydropyridine CCB (such as diltiazem or verapamil) can be substituted, but not if there is LV dysfunction *(Class IIa; Level of Evidence B)*.**
3. **If either the angina or the hypertension remains uncontrolled, a long-acting dihydropyridine CCB can be added to the basic regimen of β-blocker, ACE inhibitor, and thiazide diuretic. The combination of a β-blocker and either of the nondihydropyridine CCBs (diltiazem or verapamil) should be used with caution in patients with symptomatic CAD and hypertension because of the increased risk of significant bradyarrhythmias and HF *(Class IIa; Level of Evidence B)*.**
4. **The target BP is <130/80 mm Hg. If ventricular dysfunction is present, consideration should be given to lowering the BP even further, to <120/80 mm Hg. In patients with CAD, the BP should be lowered slowly, and caution is advised in inducing falls of DBP below 60 mm Hg. In older hypertensive individuals with wide pulse pressures, lowering SBP may cause very low DBP values (<60 mm Hg). This should alert the clinician to assess carefully any untoward signs or symptoms, especially those due to myocardial ischemia *(Class IIa; Level of Evidence B)*.**
5. **There are no special contraindications in hypertensive patients to the use of nitrates, antiplatelet or anticoagulant drugs, or lipid-lowering agents for the management of angina and the prevention of coronary events, except that in uncontrolled severe hypertension in patients who are taking antiplatelet or anticoagulant drugs, BP should be lowered without delay to reduce the risk of hemorrhagic stroke *(Class IIa; Level of Evidence C)*.**

Management of Hypertension in Patients With Acute Coronary Syndromes—Unstable Angina and NSTEMI

There are few data on the impact of antihypertensive treatment on clinical outcomes in hypertensive patients presenting with the acute coronary syndromes, and in particular, in patients with NSTEMI.

Prevalence

In 2 large, multinational, randomized trials in patients with NSTEMI, the overall prevalence of hypertension based on the patient's clinical record was 50% (54% for patients in the United States, 63% of US women, and 50% of men).[100] The prevalence ranged from 37.2% in Western Europe to 58.3% in Eastern Europe. Men and women with hypertension were older, were more likely to be black, and had a much higher prevalence of other risk factors such as diabetes mellitus, hyperlipidemia, prior MI, prior stroke, a history of HF, and prior revascularization. In 2 earlier trials in patients with NSTEMI, the prevalence of hypertension was 54% and 49.7%, respectively.[101,102] In 2 other European trials, hypertension prevalence was lower, 30.5% in the Fragmin and fast Revascularization during InStability in Coronary artery disease (FRISC) Trial in Sweden[103] and 38.5% in a recent trial from Holland (ICTUS [Invasive versus Conservative Treatment in Unstable coronary Syndrome]).[104]

Impact on Prognosis

Hypertension is integrated into various risk scores as an adverse prognostic factor. In the Thrombolysis In Myocardial Infarction (TIMI) risk score, hypertension is one of several classic risk factors for CAD, and the variable "3 or more risk factors for CAD" is an independent predictor of the composite end point of mortality and recurrent ischemic events.[105] In patients with stabilized acute coronary syndromes in the

Sibrafiban versus aspirin to Yield Maximum Protection from ischemic Heart events postacute cOroNary sYndromes (SYMPHONY) trials, hypertension was an independent predictor of death and MI at 90 days.[100] In the large Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial of glycoprotein IIb/IIIa inhibitors, hypertension was predictive of death and death due to MI on univariate but not on multivariate analyses.[101] In the Global Use of Strategies To Open occluded coronary arteries (GUSTO IIb) and PURSUIT trials,[106] a very low SBP (<91 mm Hg) was strongly associated with 48-hour and 30-day mortality, but surprisingly, there was little difference in mortality between patients who had a high SBP (≥141 mm Hg) and those with an SBP in the normal or prehypertensive range (121 to 140 mm Hg).

The limitation of all of these studies is that the correlation between BP and prognosis is based on a clinical history of hypertension or baseline BP. What the data do not provide is an evaluation of the impact on prognosis of treating hypertension during an acute episode.

General Principles of Management

The cornerstone of the management of hypertension in patients with acute coronary syndromes is the modification of the balance between myocardial oxygen supply and demand, in addition to the initiation of anticoagulant and platelet inhibitor therapy.[65,107,108] Patients with acute coronary syndromes are especially vulnerable to perturbations in this relationship, because the development of an acute coronary syndrome is a clinical manifestation of an alteration in the supply-demand equation, such that ischemia occurs at rest. Although an elevated BP increases myocardial oxygen demand, rapid and excessive lowering of the DBP has the potential to result in impairment of coronary blood flow and oxygen supply, as discussed in the section on "Primary Prevention of CAD in Hypertension." In addition, patients with acute coronary syndromes often have vasomotor instability, with an increased tendency to exaggerated responses to antihypertensive therapy

Initial management includes bed rest, continuous electrocardiographic monitoring, supplemental oxygen, morphine sulfate if pain persists, and sedation if necessary. Whether the patient should be monitored in the coronary care unit, intermediate care unit, or a general ward with monitoring capabilities will depend on the availability of facilities and the level of risk.

Anti-Ischemic and Antihypertensive Therapies

Nitroglycerin

Nitroglycerin has been a cornerstone of therapy for decades, and in the hypertensive patient, intravenous nitroglycerin is effective in the reduction of BP and symptoms.[107] Clinical trials of nitrates in non–ST-elevation acute coronary syndromes have, however, been relatively small.

Patients need to be monitored for potential adverse effects, particularly profound hypotension, which can exacerbate ischemia. Patients at increased risk include the elderly, individuals who are volume depleted, and those who have used sildenafil within 24 hours. Nitrate tolerance is a problem even within the first 24 hours, and attempts should be made to minimize this by reducing intravenous dosages and implementing intermittent dosing by nonintravenous routes once the patient is stable from an ischemic standpoint.

β-Blockers

β-Blockers are a rational choice based on their ability to reduce both heart rate and BP and thus, myocardial oxygen demand, but their widespread use was based more on logic than hard evidence, because their popularity antedated large trials.[108] However, later trials have demonstrated the benefits of β-blockers in conjunction with nitrates in patients who have not previously taken β-blocker therapy, and others provide evidence to suggest that the addition of β-blockers is helpful in patients with persistent chest pain. In patients presenting with persistent pain, and in the absence of contraindications, β-blockers should be started intravenously, followed by the use of oral β-blockers when the patient is stable.[109] The choice of a β-blocker is based on pharmacokinetic and side effect criteria, as well as physician familiarity, but in general, cardioselective (β_1-selective) β-blockers without intrinsic sympathomimetic activity are preferable. Examples are metoprolol and bisoprolol. Shorter-acting drugs, such as esmolol, may be preferred in the acute care setting. If the patient is hemodynamically unstable, the initiation of β-blocker therapy should be delayed until stabilization of cardiogenic shock or HF has been achieved. The clinical trials evidence for this is discussed in more detail in the section on "Management of Hypertension in Patients With Acute Coronary Syndromes—STEMI."

Contraindications to the use of β-blockers in acute coronary syndromes include severe first-degree heart block (electrocardiographic PR interval >0.24 second), second- or third-degree heart block, severe bronchospastic lung disease, and decompensated HF. Two recent meta-analyses concluded that cardioselective β-blockers do not produce clinically significant adverse respiratory effects in patients with mild to moderate reactive airway disease,[110,111] which suggests that β-blockers should not be withheld from these patients.

Calcium Channel Blockers

The AHA/ACC guidelines for the management of unstable angina and NSTEMI[109] suggest that in patients with continuing or frequently recurring ischemia when β-blockers are contraindicated, a nondihydropyridine CCB (verapamil or diltiazem) can be used as initial therapy in the absence of severe LV dysfunction or other contraindications. There are several randomized clinical trials that show efficacy for CCBs in acute coronary syndromes. These show that these agents prevent or relieve symptoms and the related ischemia as well as β-blockers do. The largest of these trials is the DAnish Verapamil Infarction Trial (DAVIT), which showed a trend in reducing the outcomes of death or nonfatal MI in 3447 patients with suspected acute coronary syndromes administered intravenous verapamil at admission and then orally for 1 week.[112] In the Diltiazem Reinfarction Study (DRS),[113] 576 patients were treated with diltiazem or placebo 24 to 72 hours after the onset of non–Q-wave MI. There was a significant reduction in reinfarction and refractory angina at 14 days. Similar findings were reported in the Multicenter

Diltiazem Post-Infarction Trial (MDPIT).[114] Retrospective analyses of the DAVIT and MDPIT trials have concluded that the administration of verapamil or diltiazem to patients with suspected acute coronary syndromes who have LV dysfunction has an overall detrimental effect on mortality, although some studies have shown that verapamil and diltiazem may be safe in these patients.[115,116] However, it is prudent to avoid the use of verapamil or diltiazem in patients who have LV dysfunction, and they should definitely not be used together with β-blockers in that situation.

Evidence for the use of dihydropyridine CCBs in acute coronary syndromes is based on small trials. These agents alone, or in combination with β-blockers, are effective in the management of symptoms, and there is good evidence, summarized in the previous section, that they have favorable effects on long-term mortality and recurrent infarction rates. Long-acting dihydropyridine CCBs should be used; short-acting dihydropyridine CCBs such as nifedipine can cause severe hemodynamic instability and should never be used unless in combination with a β-blocker. All CCBs have the potential to cause hypotension and conduction disturbances, particularly when used in conjunction with β-blockers. The combination of a long-acting dihydropyridine CCB and β-blocker should be used with great caution in patients with significant LV dysfunction.

ACE Inhibitors and ARBs

An ACE inhibitor should be prescribed if hypertension persists, if the patient has evidence of LV dysfunction or HF, or if the patient has diabetes mellitus.[109] Whether the drug is administered intravenously or orally will depend on the hemodynamic stability of the patient. In patients with LV dysfunction after STEMI, ARBs have been shown to be an excellent alternative. Few data are available in NSTEMI.

Diuretics

Although thiazide diuretics play a major role in the long-term control of BP, in the acute setting, diuretics are primarily used for patients with evidence of increased filling pressures, pulmonary venous congestion, or HF.

Adjunctive Therapy

The role of antithrombotic and antiplatelet therapy will not be discussed in the context of this statement. Such drugs are a pivotal aspect of therapy, and in the setting of uncontrolled hypertension, the risk of hemorrhagic stroke is increased. This provides another rationale for the aggressive control of hypertension in patients with acute coronary syndromes. The decision to pursue an invasive as opposed to a conservative approach is based on standard clinical, demographic, and angiographic criteria. Hypertension per se should not influence the decision other than indirectly, in relationship to renal function and to the presence or absence of renal artery stenosis as raising the possibility of combined coronary and renal angioplasty. It is logical, however, for BP to be stable and controlled before any intervention is begun.

Acute Severe Hypertension and "Flash" Pulmonary Edema

Such patients may have elevated biomarkers and fall under the rubric of a non–ST-elevation acute coronary syndrome. Initial therapy with intravenous nitroglycerin, furosemide, and a short-acting or intravenous ACE inhibitor is appropriate, followed by the addition of other drugs under tight control and monitoring. If tachycardia or ischemia is the predominant presentation, intravenous esmolol together with intravenous nitroglycerin is usually the first choice. BP lowering should be aggressive but requires close monitoring, particularly in the presence of ongoing ischemia or cerebral symptoms. Intravenous labetalol is helpful in some patients. Intravenous nitroprusside is used frequently, but the key is careful titration and monitoring to avoid hypotension. The risk of cyanide toxicity limits the long-term use of nitroprusside.

Conclusions

In 56 963 elderly patients with NSTEMI in the CRUSADE (Coronary Revascularization UltraSound Angioplasty DEvice trial) Registry,[117] the use of guidelines-recommended care was associated with improved in-hospital outcomes in patients treated invasively or conservatively. The frequency of hypertension was 61.8% in patients >65 years of age and approximately 75% in an older age group. Age had a relatively modest impact on the use of aspirin and β-blockers, but the use of antithrombotics and platelet inhibitors was considerably less in the elderly.

Hypertension will continue to be highly prevalent in populations with acute coronary syndromes, many of whom are elderly. Nonetheless, the majority will respond to standard methods of hypertension control. The benefits of treating hypertension in the acute coronary syndrome setting are logical, but perhaps the major impact on long-term morbidity and mortality depends on the efficacy of continued outpatient BP control once effective therapy has been initiated in the hospital.

Recommendations

1. **In unstable angina or NSTEMI, the initial therapy of hypertension should include short-acting β1-selective β-blockers without intrinsic sympathomimetic activity, usually intravenously, in addition to nitrates for symptom control. Oral β-blockers can be substituted at a later stage of the hospital stay *(Class IIa; Level of Evidence B)*. Alternatively, oral β-blockers may be started promptly without prior use of intravenous β-blockers *(Class I; Level of Evidence A)*. If the patient is hemodynamically unstable, the initiation of β-blocker therapy should be delayed until stabilization of HF or shock has been achieved. Diuretics can be added for BP control and for the management of HF *(Class I; Level of Evidence A)*.**
2. **If there is a contraindication to the use of a β-blocker, or if the patient develops intolerable side effects of a β-blocker, then a nondihydropyridine CCB, such as verapamil or diltiazem, may be substituted, but not if there is LV dysfunction. If the angina or the hypertension is not controlled with a β-blocker alone, then a longer-acting dihydropyridine CCB may be added. A thiazide diuretic can**

also be added for BP control *(Class I; Level of Evidence B)*.

3. **If the patient is hemodynamically stable, an ACE inhibitor *(Class I; Level of Evidence A)* or ARB *(Class I; Level of Evidence B)* should be added if the patient has an anterior MI, if hypertension persists, if the patient has evidence of LV dysfunction or HF, or if the patient has diabetes mellitus.**
4. **The target BP is <130/80 mm Hg. However, in patients with an elevated DBP and acute coronary syndrome, the BP should be lowered slowly, and caution is advised in inducing falls of DBP below 60 mm Hg. In older hypertensive individuals with wide pulse pressures, lowering SBP may cause very low DBP values (<60 mm Hg). This should alert the clinician to assess carefully any untoward signs or symptoms, especially those due to worsening myocardial ischemia *(Class IIa; Level of Evidence B)*.**
5. **There are no special contraindications in hypertensive patients to the use of nitrates, anticoagulants, antiplatelet drugs, or lipid-lowering agents for the management of acute coronary syndromes. For the same reason, BP should be lowered without delay in patients with uncontrolled hypertension who are taking antiplatelet or anticoagulant drugs *(Class IIa; Level of Evidence C)*.**

Management of Hypertension in Patients With Acute Coronary Syndromes—STEMI

Although a major risk factor for cardiovascular disease, the impact of hypertension on STEMI outcomes is not well described. Thus, although acute treatment for STEMI may include many antihypertensive drugs, little has been published on the appropriate treatment of hypertension at the time of presentation with STEMI.

Prevalence and Prognostic Impact

As in the unstable angina/NSTEMI cohort described in the previous section, a history of hypertension has been found to increase the risk of mortality after STEMI.[118] However, the prognostic significance of BP on presentation for STEMI is not well characterized. Although several prognostic scores for STEMI include BP, they most frequently describe low BP on presentation as a negative predictor of survival. Yet, because of the increased risk of intracranial hemorrhage in patients with uncontrolled hypertension at presentation, hypertension remains a relative contraindication to fibrinolysis for STEMI.[95] Thus, both acute hypotension and hypertension are associated with an increased risk of adverse outcomes in the setting of acute coronary syndromes. In reviewing the current evidence on the management of hypertension, few data are available to specifically address the issue of risk stratification; however, there is substantial evidence to support (or not) the use of various classes of antihypertensive agents.

General Principles of Management

As in the case of unstable angina/NSTEMI, the cornerstone of the management of hypertension in patients with acute coronary syndromes is modification of the balance between myocardial oxygen supply and demand, in addition to the initiation of antithrombotic and platelet inhibitor therapy. Patients with acute coronary syndromes are particularly vulnerable to perturbations in this relationship, because the development of an acute coronary syndrome is a clinical manifestation of an alteration in the supply-demand equation such that ischemia occurs at rest. Although an elevated BP increases myocardial oxygen demand, rapid and excessive lowering of the DBP can result in impairment in coronary blood flow and oxygen supply, as discussed in the section "Primary Prevention of CAD in Hypertension."

Anti-Ischemic and Antihypertensive Therapies

Nitroglycerin

Nitroglycerin has historically been the preferred choice for management of both ischemic discomfort in acute coronary syndromes and acute hypertension; however, the level of evidence for these practices is not high. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-3 and International Study of Infarct Survival (ISIS)-4 trials included almost 80 000 patients and found no difference in mortality with the use of nitrates (7.0% for those treated versus 7.2% who received placebo in GISSI-3, and 7.3% versus 7.5%, respectively, in ISIS-4).[119,120] Thus, the ACC/AHA guidelines do not recommend the use of nitroglycerin to reduce events but only to relieve ischemic pain or acute hypertension, or to manage pulmonary congestion, at a "C" level of evidence. Furthermore, the guidelines caution that nitroglycerin should not be used at the expense of agents with proven benefits on outcomes, such as β-blockers or ACE inhibitors (see below), particularly in the convalescent stage.[95]

β-Blockers

As in the unstable angina/NSTEMI setting, β-blockers are a logical choice in an attempt to reduce heart rate, contractility, and thereby oxygen demand. Their benefits when initiated at discharge and continued long term have been shown in multiple trials,[121,122] and early intravenous use of β-blockers was seen in the TIMI II-B study to reduce ischemic events versus later use.[123] Early intravenous β-blockade was also supported in the ISIS-1 trial and by a meta-analysis of 30 trials in nearly 30 000 patients.[124,125] The recent publication of the COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial)/Chinese Cardiac Study (CCS)-2 provided additional insight into β-blocker strategies.[126] The investigators randomized 45 852 acute MI patients to intravenous then oral β-blockers at presentation versus placebo and assessed the coprimary outcomes of (1) the composite of death, reinfarction, or cardiac arrest and (2) death due to any cause. At discharge or up to 4 weeks after randomization, neither outcome was reduced with metoprolol; however, the COMMIT trial did demonstrate a reduction in reinfarction (2.0% versus 2.5%) and ventricular fibrillation (2.5% versus 3.0%), but at the expense of an increase in cardiogenic shock (5.0% versus 3.9%). The excess risk of shock was highest in the first 2 days of hospitalization, especially in patients with evidence of hemodynamic instability at presentation. In a subset analysis of patients with hypertension (SBP >140 mm Hg), there were no statisti-

cally significant differences between the β-blocker and placebo arms with respect to the composite primary end point, death, or cardiogenic shock alone, although there was a trend in favor of the β-blocker. The conclusion is that early intravenous β-blocker therapy is beneficial but should be reserved for low-risk patients and delayed a few days until after patients with signs of HF or shock have been stabilized. Hypertension is not a contraindication to early intravenous β-blockade in the absence of hemodynamic instability.

ACE Inhibitors

ACE inhibitors have also been tested as early interventions for acute MI. In the setting of STEMI, ischemic/infarcted muscle increases wall stress, which causes the myocardium to remodel and dilate, a process that begins at the time of initial ischemic insult. ACE inhibitors could reduce infarct expansion/remodeling and chamber dilatation, thereby preventing sequelae such as ventricular arrhythmia, failure, or rupture.[119,127,128] The GISSI-3, ISIS-4, and CCS-1 trials demonstrated a benefit to early administration of ACE inhibitors, with absolute reductions in mortality of 0.8%, 0.5%, and 0.5%, respectively, seen as early as 4 weeks after AMI.[119,120,129] This effect of early (within 24 hours) ACE inhibitor therapy is particularly pronounced in higher-risk patients: those with anterior or particularly large infarcts, previous infarction, HF, depressed LV ejection fraction (LVEF), and tachycardia.[95,118,125]

Angiotensin Receptor Blockers

ARBs are a useful alternative to ACE inhibitors. The VALIANT trial[89] randomized patients with LV dysfunction and/or HF within 10 days after acute MI to additional therapy with valsartan, captopril, or both and monitored them for ≈2 years. Valsartan was as effective as captopril for reducing cardiovascular events in these high-risk patients; however, the combination of valsartan with captopril increased the rate of adverse events without improving survival. On the other hand, the OPTIMAAL trial showed a trend toward increased mortality in patients receiving 50 mg of losartan once daily over patients receiving 50 mg of captopril 3 times daily,[88] but these negative results may be due to inadequate dosing.

Aldosterone Antagonists

Both spironolactone and eplerenone lower BP. These agents had a secondary protective effect in patients with severe HF in the RALES study[90] and in patients with LV dysfunction (LVEF ≤40%) after MI in EPHESUS.[91] In the EPHESUS trial, there was a 15% reduction in mortality with eplerenone at 16 months. A reduction in mortality was seen as early as 30 days, which emphasizes the benefit of early inhibition of the RAAS and the clinical need to start therapy before discharge.[130] However, aldosterone antagonists should be avoided in patients with elevated serum creatinine levels (≥2.5 mg/dL in men, ≥2.0 mg/dL in women) or elevated potassium levels (≥5.0 mEq/L), because there is a serious risk of hyperkalemia with use of these agents in patients with an estimated creatinine clearance of <50 mL/min.[95]

Calcium Channel Blockers

In general, CCBs have not been found to be useful in the setting of acute STEMI. Clinical trials of the dihydropyridine class, specifically the rapid-release form of nifedipine, have indicated no benefit and a potential increase in mortality in patients treated with this agent.[131] This conclusion was independent of the reperfusion strategy selected. The nondihydropyridine agents diltiazem and verapamil have also been disappointing in the early-MI setting and are not recommended for patients with STEMI.[95,132,133] However, no harm was observed in 1 study with verapamil in patients with HF after an acute MI, all of whom were treated with ACE inhibitors.[112] Long-acting dihydropyridine CCBs are preferred after an acute MI for patients with continuing ischemic discomfort or rapid ventricular arrhythmias who are unresponsive to β-blockers or in whom β-blockers are contraindicated. Nondihydropyridine CCBs (diltiazem and verapamil) should be avoided in patients with modest to severe HF or bradyarrhythmias.[95]

Diuretics

Although diuretics have a major role in the treatment of chronic hypertension and exacerbations of acute HF, their use is not supported in the acute STEMI setting.

Acute Severe Hypertension and "Flash" Pulmonary Edema

The same principles apply when this occurs in the setting of STEMI as when it occurs in unstable angina/NSTEMI. Refer to the discussion above ("Management of Hypertension in Patients With Acute Coronary Syndromes—Unstable Angina and NSTEMI").

Conclusions

Despite clear evidence of reductions in morbidity and mortality with several of the above agents, research from the National Registry of Myocardial Infarction and the Cooperative Cardiovascular Project has shown that only a small fraction of patients are getting them.[134,135] Although hypertension in STEMI has not yet been shown to have as profound a predictive value as hypotension, it still provides an important opportunity for physicians to improve outcomes in such patients. Careful selection of therapies in the appropriate patients can improve symptoms, cardiac function, and mortality and decrease complications during and after hospitalization.

Recommendations

1. **In STEMI, the principles of therapy for hypertension are similar to those for unstable angina and NSTEMI as described above, with some exceptions. Initial therapy of hypertension can include short-acting β1-selective β-blockers without intrinsic sympathomimetic activity, usually intravenously, in addition to nitrates for symptom control *(Class IIa; Level of Evidence B)*. However, if the patient is hemodynamically unstable, the initiation of β-blocker therapy should be delayed until stabilization of HF or shock has been achieved. Oral β-blockers can be substituted at a later stage of the hospital stay. Alternatively, oral β-blockers may be**

started promptly without prior intravenous β-blockers *(Class I; Level of Evidence A)*. Diuretics can be added for BP control and for management of HF *(Class I; Level of Evidence A)*.

2. **An ACE inhibitor *(Class I; Level of Evidence A)* or ARB *(Class I; Level of Evidence B)* should be administered early in patients with STEMI and hypertension, particularly in anterior MI, or if hypertension persists or there is LV dysfunction, HF, or diabetes mellitus. ACE inhibition has been found to be particularly beneficial in patients in whom the infarct is large and/or there is a history of previous infarction, HF, and tachycardia. ACE inhibitors and ARBs should not be given together because there is an increase in the incidence of adverse events without improving survival.**
3. **Aldosterone antagonists may be useful in the management of STEMI with LV dysfunction and HF and may have an additive BP-lowering effect. Serum potassium levels must be monitored. These agents should be avoided in patients with elevated serum creatinine levels (≥2.5 mg/dL in men, ≥2.0 mg/dL in women) or elevated potassium levels (≥5.0 mEq/L) *(Class I; Level of Evidence A)*.**
4. **CCBs do not reduce mortality rates in the setting of acute STEMI and can increase mortality if there is depressed LV function and/or pulmonary edema. Long-acting dihydropyridine CCBs can be used when β-blockers are contraindicated or inadequate to control angina, or as adjunct therapy for BP control. Nondihydropyridine CCBs may be used for the treatment of patients with supraventricular tachycardia but should not be used in patients with bradyarrhythmias or impaired LV function *(Class IIa; Level of Evidence B)*.**
5. **As in patients with unstable angina/NSTEMI, the target BP in patients with STEMI is <130/80 mm Hg; however, in patients with an elevated DBP and STEMI, the BP should be lowered slowly, and caution is advised in inducing falls of DBP below 60 mm Hg. In older hypertensive individuals with wide pulse pressures, lowering SBP may cause very low DBP values (<60 mm Hg). This should alert the clinician to assess carefully any untoward signs or symptoms, especially those due to worsening myocardial ischemia *(Class IIa; Level of Evidence B)*.**
6. **There are no special contraindications in hypertensive patients to the use of nitrates, anticoagulant and antiplatelet drugs, or lipid-lowering agents for the management of STEMI. Uncontrolled hypertension is a contraindication to fibrinolytic therapy because of the risk of intracranial hemorrhage. For the same reason, BP should be lowered without delay in patients with uncontrolled hypertension who are taking antiplatelet or anticoagulant drugs *(Class IIa; Level of Evidence C)*.**

Management of Hypertension in HF of Ischemic Origin

Although guidelines from the ACC and the AHA exist for the treatment of chronic HF,[97,136] evidence on which to base guidelines for the treatment of hypertension in patients with HF of ischemic origin is limited. On the basis of information from the Acute Decompensated Heart Failure National Registry (ADHERE),[137] ≈75% of patients hospitalized with HF had hypertension, with most having SBPs >140 mm Hg.

Hypertension and HF

Most patients with HF have arterial hypertension.[138] Not only is hypertension an important concomitant disorder, but it also contributes to the pathogenesis of systolic and diastolic HF. Hypertension is a major risk factor for IHD and can lead to the development of HF by causing LV hypertrophy, impaired cardiac myocyte contractility, ventricular chamber remodeling, and eventually diastolic and systolic dysfunction.[139–141]

Demographics

Patients presenting with HF are more likely to be older and hypertensive, and more than half have a normal LVEF.[137,142] Early investigations of patients with HF, such as the Framingham Heart Study,[143] cited hypertension as the most frequent comorbidity. Approximately 15% of participants in the Studies Of Left Ventricular Dysfunction (SOLVD) trial had a DBP >90 mm Hg at enrollment.[144] In a population-based epidemiological trial in Olmstead County, Minnesota, ≈50% of patients presenting with new-onset HF had hypertension.[145]

However, recent randomized trials have probably underestimated the contribution of hypertension to the development and progression of HF, possibly because elderly patients are often not included in clinical trials of HF. Of note, HF symptoms are rare in hypertensive individuals whose BP is well controlled and who have not sustained an MI.[146]

Hypertension and Systolic Dysfunction

Initially, concentric hypertrophy of the LV compensates for pressure overload and normalizes systolic wall stress. This adaptive hypertrophy is accompanied by structural modifications of the cardiac muscle, including alterations in gene expression, loss of cardiomyocytes, defective vascular development, and fibrosis. Thus, the compensatory response may transition to HF with progressive contractile dysfunction.[147] In the second stage, CAD causes myocardial ischemia or MI, which results in HF. BP falls as HF develops, such that the contribution of hypertension to the HF syndrome may be underestimated.

The mechanisms by which increased LV mass leads to depressed LVEF remain ill defined. Traditionally, an MI has been viewed as an obligatory event in the transition to depressed systolic function. Because MI occurs in 16% of those who develop depressed LVEF compared with 3% of those who do not, it is an important risk factor.[148] However, there must be other mechanisms, because increased LV mass remains associated with the development of depressed LVEF even in patients free of clinically manifest CAD, including MI. With antihypertensive treatment, the incidence of LVH in

treated patients is reduced by 35%, and the development of HF is reduced by 52%.[146]

CAD and Acute HF

Ischemia may trigger acute pulmonary edema. The majority of patients with flash pulmonary edema have preserved systolic function.[137,149–153] These patients are generally elderly and have severe CAD, typically with 1 occluded vessel and a severely stenosed coronary artery supplying collateral flow.[152–154] Patients with preserved systolic function and LV hypertrophy are particularly susceptible to this type of episode because of their reduced ventricular distensibility, in which small changes in ventricular volume status can lead to large changes in filling pressures. This abnormal diastolic pressure-volume relationship may also explain why these patients frequently improve quickly with diuresis and lowering of BP.[155]

Therapeutic Strategies

The therapeutic goals in patients presenting with HF are to reverse hemodynamic abnormalities, relieve symptoms, and initiate treatments that will decrease disease progression and improve survival.

Behavioral Modifications

Sodium restriction is important in the management of both hypertension and LV dysfunction. Exercise training[156,157] has been shown to reduce recurrent cardiac events in patients with LV dysfunction from ischemic causes. For patients with HF, close medical supervision and careful monitoring of the BP response to exercise and of the ECG for ventricular arrhythmias are appropriate.[158,159]

Diuretics

Thiazide diuretics are effective in preventing HF in hypertensive patients.[67] Thiazide diuretics are the drugs of choice in patients with mild HF because of a more sustained natriuretic and diuretic action than loop diuretics, particularly in those individuals in whom BP control may be more important than correction of volume overload.

In more severe HF, diuretics are used to reverse volume overload and associated symptoms. Usually loop diuretics, such as furosemide and torsemide, are used because they produce a greater diuresis for the same degree of natriuresis; they work even in the presence of renal impairment, a frequent accompaniment of severe HF; and their dose-response characteristics are linear and steep, which allows for escalation to high doses.

By inducing sodium and water loss, diuretics also activate several adverse mechanisms. There may be a decrease in right ventricular filling pressure, with a fall in stroke volume and activation of the RAAS and the sympathetic nervous system,[160] effects that would be expected to be harmful.[161,162] This problem is avoided by combining diuretic therapy with an ACE inhibitor or ARB, a β-blocker, and/or an aldosterone antagonist, all of which have been shown to provide effective therapy in HF.

ACE Inhibitors

ACE inhibitors are thought to reduce the remodeling that occurs after MI,[163] improve ischemic preconditioning, reverse angiotensin II–induced vasoconstriction and inotropy, prevent the depletion of high-energy phosphate stores, enhance nitric oxide release through prevention of bradykinin breakdown,[164] and reduce blood coagulability through the endothelial release of tissue plasminogen activator.[165] ACE inhibitors have been shown in many trials to be beneficial in patients with LV dysfunction of ischemic origin. The Trandolapril Cardiac Evaluation (TRACE) trial showed a 7% absolute reduction in mortality rate.[166,167] In the Acute Infarction Ramipril Efficacy (AIRE) trial,[168] ramipril administered 3 to 7 days after MI reduced the relative mortality risk by 27% in the total cohort, by 15% in normotensive subjects, and by 41% in hypertensive subjects, which supports the particular importance of ACE inhibition in hypertensive patients with LV dysfunction in the post-MI period. In the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial, mortality was significantly lower in patients with HF who received a high dose of lisinopril (32.5 to 35 mg/d) than in those treated with a low dose of lisinopril (2.5 to 5 mg/d).[169] However, the message has not gotten through to clinicians as well as it should; in the ADHERE registry, only 73% of eligible patients with LV dysfunction were prescribed an ACE inhibitor, and in the post-MI setting, this number is probably lower.[137]

Angiotensin Receptor Blockers

The VALIANT trial found valsartan to be noninferior to captopril, although it did not show superiority.[89] The Evaluation of Losartan In The Elderly (ELITE)-II trial compared the efficacy of losartan 50 mg/d with captopril 150 mg/d and found that the rates of all-cause mortality and sudden death or resuscitated arrests for the losartan group were not significantly different from those for the captopril group.[170] The Valsartan Heart Failure Trial (Val-HeFT) assessed the efficacy of valsartan at doses of up to 320 mg/d added to standard therapy for reducing morbidity and mortality in patients with HF.[171] Patients receiving valsartan demonstrated a 13.2% reduction in the combined end point of cardiovascular mortality and morbidity compared with patients receiving placebo. Additional insights into the value of ARBs are provided by the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program.[172–175] In patients not receiving ACE inhibitors because of previous intolerance, the use of candesartan was associated with a significant reduction in the primary composite end point of cardiovascular death and hospital readmission for HF compared with placebo.[172]

In the combination arm of VALIANT, valsartan and captopril together showed no increased effect over captopril alone and had a higher incidence of discontinuation due to adverse effects.[89] These results differed from those of the CHARM-Added trial, in which patients with stable LV dysfunction benefited from the combination of an ACE inhibitor and the ARB candesartan.[176] The lack of superiority of the combination treatment in the VALIANT trial was likely due to the fact that ACE inhibitors and ARBs were titrated aggressively at the same time in the early post-MI period, which resulted in more side effects. In the stable HF patients undergoing an established ACE inhibitor therapy, the

CHARM trial showed that the addition of an ARB was well tolerated and beneficial. This is a strategy that could be used to control BP if needed.

Nitrates

Nitrate tolerance has limited the ability of long-term nitrates alone to be effective as antihypertensive agents. The addition of hydralazine to a nitrate reduces this tolerance. Interest in this combination for HF has been revived by a recent trial that suggested that a combination of a fixed dose of both isosorbide dinitrate and hydralazine provides additional benefit in black patients with advanced HF. The trial was stopped early because of a significantly higher mortality rate in the placebo group than in the group receiving isosorbide dinitrate plus hydralazine (10.2% versus 6.2%, $P=0.02$).[177]

β-Adrenoreceptor Blockers

β-Blockers lower BP and are negatively inotropic and chronotropic. They therefore alleviate ischemia and angina in addition to lowering BP. The role of β-blockers in the management of patients with HF is well established. The Metoprolol CR/XL Randomized Intervention Trial in Heart failure (MERIT-HF) randomized patients with New York Heart Association class II to IV HF symptoms to receive metoprolol succinate versus placebo.[178] This trial was stopped prematurely because of a 34% reduction in mortality in the metoprolol arm.

Four clinical trials of carvedilol in HF were stopped prematurely because of a highly significant 65% reduction in mortality in patients treated with carvedilol compared with placebo.[179] The CarvedilOl ProspEctive RaNdomIzed CUmulative Survival (COPERNICUS) trial assessed patients with severe HF symptoms who were clinically not volume overloaded and who had an LVEF of <25%. Compared with placebo, carvedilol reduced the mortality risk at 12 months by 38% and the risk of death or hospitalization for HF by 31%.[180] The Multicenter Oral Carvedilol Heart failure Assessment (MOCHA) trial demonstrated that this effect of carvedilol is dose-related, with higher doses of 25 mg twice daily showing greater LV functional and clinical superiority than 6.25 mg twice daily, a dose that was superior to placebo.[181] Another longer-acting β-blocker, bisoprolol, showed similar long-term benefit on survival in patients with HF. The Cardiac Insufficiency Bisoprolol Study (CIBIS-II) showed a 32% reduction in all-cause mortality in bisoprolol-treated patients with New York Heart Association class III or IV HF caused by ischemic and nonischemic cardiomyopathy at median follow-up of 1.3 years. In that trial, sudden deaths were reduced by 44% in the bisoprolol-treated group, whereas pump-failure deaths were reduced by 26%.[182] Although all 3 of these agents (metoprolol, carvedilol, and bisoprolol) are beneficial in patients with HF, the Carvedilol or Metoprolol European Trial (COMET) demonstrated a 17% greater mortality reduction in favor of carvedilol compared with metoprolol XL, with mean daily doses of 85 and 42 mg/d, respectively.[183] Carvedilol may be particularly appealing because of its additional α-blocking properties. In addition, there may be a more favorable effect on glycemic control. As a result of these studies, β-blockers are recommended for the long-term management of patients with hypertension-related LV systolic dysfunction.

Aldosterone Receptor Antagonists

Aldosterone has been shown to promote myocardial fibrosis. Long-term treatment with ACE inhibitors has not been associated with suppression of plasma aldosterone levels. This had led to an interest in evaluating aldosterone receptor antagonists as adjunctive therapy to ACE inhibition in patients with HF. RALES reported the effect of adding the competitive aldosterone antagonist spironolactone versus placebo to standard HF therapy in patients with stage 3 (New York Heart Association class III or IV) HF. There was a 30% reduction in total mortality with spironolactone.[90] Eplerenone, a selective aldosterone inhibitor, showed similar survival benefit when evaluated in the EPHESUS trial. Patients with an LVEF of <40% were randomly assigned at 3 to 14 days after MI to therapy with eplerenone or placebo. During a mean follow-up of 16 months, eplerenone significantly improved mortality by ≈15%.[91] Although these trials did not specifically evaluate patients with hypertension and HF, the improvement in relative risk with eplerenone was greater in the subgroup with a history of hypertension than in normotensive subjects,[91] which suggests that these agents may be particularly beneficial in patients with hypertension and HF.

Target BP

BP targets in HF have not been firmly established, but in most successful trials, SBP was lowered to the range of 110 to 130 mm Hg. One trial, COPERNICUS,[180] demonstrated benefits of carvedilol in patients with entry criteria that included an SBP as low as ≥85 mm Hg and who had a mean pretreatment BP of 123/76 mm Hg, which suggests that lower BPs (SBP <120 mm Hg) may be desirable in some patients. On this basis, we make the recommendation that the target BP in patients with HF should be <130/80 mm Hg, but we also suggest that consideration should be given to lowering the BP even further, to <120/80 mm Hg.

Drugs to Avoid

There are several classes of drugs that should be avoided in patients with ischemic systolic HF with hypertension. Because of their negative inotropic properties and the increased likelihood of worsening HF symptoms, nondihydropyridine CCBs such as diltiazem and verapamil should be avoided.[184] The dihydropyridine CCB amlodipine appeared to be safe in patients with severe systolic HF in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial,[185] as was felodipine as supplementary vasodilator therapy in the Vasodilator-Heart Failure Trial (V-HeFT) III.[186] Although clonidine is an effective antihypertensive agent, another drug in the same class, moxonidine, was associated with increased mortality in patients with HF,[187] and therefore clonidine should probably also be avoided. In the ALLHAT trial, the doxazosin arm of the trial was discontinued because of a 2.04-fold increase in relative risk of developing HF compared with chlorthalidone treatment.[188] Although there are several caveats about extrapolating these data to the management of hypertension in patients with HF, α-blockers should be used only if other agents used for the management of hypertension

and HF are inadequate to achieve good BP control, and even then, they should be used with caution.

Recommendations

1. **The treatment of hypertension in patients with HF should include behavioral modification, such as sodium restriction, and a closely monitored exercise program *(Class I; Level of Evidence C)*. Other nonpharmacological approaches are the same as for patients without HF.**
2. **Drugs that have been shown to improve outcomes for patients with HF generally also lower BP. Patients should be treated with diuretics, ACE inhibitors (or ARBs), β-blockers, and aldosterone receptor antagonists *(Class I; Level of Evidence A)*.**
3. **Thiazide diuretics should be used for BP control and to reverse volume overload and associated symptoms. In severe HF, or in patients with severe renal impairment, loop diuretics should be used for volume control, but these are less effective than thiazide diuretics in lowering BP. Diuretics should be used together with an ACE inhibitor or ARB and a β-blocker *(Class I; Level of Evidence C)*.**
4. **Studies have shown equivalence of benefit of ACE inhibitors and the ARBs candesartan or valsartan in HF. Either class of agents is effective in lowering BP. Drugs from each class can be used together, provided that the patient is hemodynamically stable and not in the immediate post-MI period *(Class I; Level of Evidence A)*.**
5. **Among the β-blockers, carvedilol, metoprolol succinate, and bisoprolol have been shown to improve outcomes in HF and are effective in lowering BP *(Class I; Level of Evidence A)*.**
6. **The aldosterone receptor antagonists spironolactone and eplerenone have been shown to be beneficial in HF and should be included in the regimen if there is severe HF (New York Heart Association class III or IV, or LVEF <40% and clinical HF). One or the other may be substituted for a thiazide diuretic in patients requiring a potassium-sparing agent. If an aldosterone receptor antagonist is administered with an ACE inhibitor or an ARB or in the presence of renal insufficiency, the serum potassium should be monitored frequently. These drugs should not be used, however, if the serum creatinine level is ≥2.5 mg/dL in men or ≥2.0 mg/dL in women, or if the serum potassium level is ≥5.0 mEq/L. Spironolactone or eplerenone may be used together with a thiazide diuretic, particularly in patients with refractory hypertension *(Class I; Level of Evidence A)*.**
7. **Consider the addition of hydralazine/isosorbide dinitrate to the regimen of diuretic, ACE inhibitor or ARB, and β-blocker in black patients with NYHA class III or IV heart failure *(Class I; Level of Evidence B)*. Others may benefit similarly, but this has not yet been tested.**
8. **Drugs to avoid in patients with HF and hypertension are nondihydropyridine CCBs (such as verapamil and diltiazem), clonidine, and moxonidine (*Class III; Level of Evidence B*). α-Adrenergic blockers, such as doxazosin, should be used only if other drugs for the management of hypertension and HF are inadequate to achieve BP control at maximum tolerated doses *(Class IIa; Level of Evidence B)*.**
9. **The target BP is <130/80 mm Hg, but consideration should be given to lowering the BP even further, to <120/80 mm Hg. In patients with an elevated DBP who have CAD and HF with evidence of myocardial ischemia, the BP should be lowered slowly, and caution is advised in inducing falls of DBP below 60 mm Hg if the patient has diabetes mellitus or is over the age of 60 years. In older hypertensive individuals with wide pulse pressures, lowering SBP may cause very low DBP values (<60 mm Hg). This should alert the clinician to assess carefully any untoward signs or symptoms, especially those due to myocardial ischemia and worsening HF *(Class IIa; Level of Evidence B)*.**

Appendix

Men

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total Cholesterol	Points Age 20-39	40-49	50-59	60-69	70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
280	11	8	5	3	1

	Points Age 20-39	40-49	50-59	60-69	70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	Untreated	Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
160	2	3

Point Total	10-Year Risk %
<0	<1
0-4	1
5-6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
17	30

10-Year risk _____%

Women

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total Cholesterol	Points Age 20-39	40-49	50-59	60-69	70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
280	13	10	7	4	2

	Points Age 20-39	40-49	50-59	60-69	70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	Untreated	Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
160	4	6

Point Total	10-Year Risk %
<9	<1
9-12	1
13-14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
25	30

10-Year risk _____%

Calculating a 10-year risk for coronary heart disease using Framingham point scores. Reprinted from The National Heart, Lung, and Blood Institute as a part of the National Institutes of Health and the US Department of Health and Human Services, NIH Publication No. 01-3305. Available at: http://www.nhlbi.nih.gov/guidelines/cholesterol/risk_tbl.htm.

Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
Clive Rosendorff	Veterans Health Administration; Mount Sinai School of Medicine	Bristol-Myers Squibb; Merck; Daiichi Sankyo Pharmaceutical; AstraZeneca	None	AstraZeneca; Cardiovascular Therapeutics; Schering-Plough	None	Siemens Diagnostics	None
Henry R. Black	Rush University Medical Center	Pfizer	None	Novartis; Pfizer; Sanofi; Bristol-Myers Squibb	None	Intercure; MSD; Myogen; Novartis; Pfizer; Sanofi	None
Christopher P. Cannon	TIMI Study Group, Brigham and Women's Hospital	Accumetrics; AstraZeneca; Merck; Merck/Schering-Plough Partnership; Schering-Plough	None	Accumetrics; AstraZeneca; Bristol-Myers Squibb; Genentech; Merck; Merck/Schering-Plough Partnership; Pfizer; Sanofi-Aventis; Schering-Plough	None	Abbott; Alnylam; Arena; AstraZeneca; Biosite; Bristol-Myers Squibb; Eisai; GlaxoSmithKline; Johnson & Johnson; Merck; Merck/Schering-Plough Partnership; Pfizer; Sanofi-Aventis; Schering-Plough; Tethys; Vertex	None
Bernard J. Gersh	Mayo Clinic	AstraZeneca; Bristol-Myers Squibb; Boston Scientific; Abbott Laboratories; Cardiovascular Therapeutics Inc	None	None	None	None	None
Joel Gore	University of Massachusetts Medical Center	Sanofi-Aventis; Medicine Group	None	None	None	None	None
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Patrick T. O'Gara	Brigham and Women's Hospital	None	None	None	None	Boston Scientific	None
Suzanne Oparil	University of Alabama	Abbott Laboratories; Boehringer Ingelheim; Bristol-Myers Squibb; Daiichi Sankyo; Merck; Novartis; Pfizer; Sanofi-Aventis	None	Boehringer Ingelheim; Bristol-Myers Squibb; Daiichi Sankyo; Forest Laboratories; Merck; Novartis; Pfizer	Member, Board of Directors, Encysive Pharmaceuticals	Bristol-Myers Squibb; Merck; Sanofi-Aventis; Novartis; Pfizer; The Salt Institute	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit.

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Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Robert M. Carey	University of Virginia	None	None	None	None	None	None	None
Douglas S. Schocken	University of South Florida	None	None	None	None	None	None	None
Michael Weber	SUNY Downstate	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit.

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KEY WORDS: AHA Scientific Statements ■ hypertension ■ coronary disease ■ angina ■ myocardial infarction ■ heart failure ■ heart diseases