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AHA/ACC/ASH SCIENTIFIC STATEMENT

Treatment of Hypertension in Patients With Coronary Artery Disease

A Scientific Statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension

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This is an update of the American Heart Association (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," published in 2007 (1). A number of important

studies have been published since that date that serve to modify or at least to further refine the recommendations of that statement, so an update was considered appropriate and timely. Because an AHA/American College of Cardiology (ACC)/American Society of Hypertension guideline on the treatment of hypertension in primary prevention is in process, this document is concerned with the epidemiology of hypertension and its treatment in secondary prevention, specifically in the setting of coronary artery disease (CAD).

Epidemiological studies have established a strong association between hypertension and 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 for the prevention and management of ischemic heart disease (IHD):

- What are the appropriate systolic blood pressure (SBP) and diastolic blood pressure (DBP) targets in patients 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 secondary prevention of IHD?
- Which antihypertensive drugs should be used in patients who have established CAD with stable angina pectoris, in those with acute coronary syndrome (ACS), which includes unstable angina pectoris (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI), and in those with heart failure (HF) caused by CAD?

This scientific statement summarizes the published data relating to the treatment of hypertension in the context of CAD prevention and management. It 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. When data are meager or lacking, the writing group has proposed consensus recommendations and has highlighted opportunities for well-designed prospective clinical trials to fill knowledge gaps.

All of the discussion and recommendations refer to adults. The writing committee has not addressed hypertension or IHD in the pediatric age group. In addition, there is no discussion of the different modes of assessing BP, including 24-hour ambulatory BP monitoring. These were the subject of an AHA scientific statement in 2005 (2).

Recommendations, with levels of evidence, have been developed according to the AHA format shown in **Table 1**.

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 each section should provide a stand-alone description of the recommendations and their justification independently 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 this 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 **Tables 2 and 3**.

1. RELATIONSHIP BETWEEN HYPERTENSION AND CAD

1.1. Epidemiology of Hypertension and CAD

Hypertension is a major independent risk factor for CAD for all age/race/sex groups. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (3) uses the traditional definition of hypertension as an SBP of ≥140 mm Hg or a DBP of ≥90 mm Hg and/or the current use of antihypertensive medication. With this definition, an estimated 65 million adult Americans, or nearly one fourth of the adult population of the United States, have hypertension. Another quarter of the population have prehypertension, defined as an SBP of 120 to 139 mm Hg or a DBP of 80 to 89 mm Hg.

The forms of BP elevation differ as a function of age, with DBP elevation predominating in young hypertensive individuals and systolic hypertension, often in isolation (isolated systolic hypertension), emerging in older age. The prevalence of hypertension is thus directly proportional to the age of the population, with more than one-half of Americans >65 years of age having a high BP. The Framingham Heart Study has estimated the remaining lifetime risk of developing hypertension at ≈90% for men and women not yet hypertensive by middle age (4). In addition, there is a change with age in the relative importance of SBP and DBP as risk indicators. Before 50 years of age, DBP is the major predictor of IHD risk, whereas after 60 years of age, SBP is more important (5). It is important to note that, in this population ≥60 years of age, DBP becomes inversely related to CAD risk and pulse pressure becomes the strongest predictor for CAD. In a meta-analysis of 61 studies that included almost 1 million adults (6), BP was related to fatal CAD over the BP range of 115/75 to 185/115 mm Hg for all ages. Overall, each increase in SBP of 20 mm Hg (or each 10-mm Hg increase in DBP) doubles the risk of a fatal coronary event.

Epidemiological studies have also shown that an elevated BP is the most important determinant of the risk

TABLE 1 Applying Classification of Recommendations and Levels of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/Test: COR III: No benefit — Not Helpful; COR III: Harm — Excess Cost w/o Benefit or Harmful Treatment: No Proven Benefit; Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/administered/other; is not useful/beneficial/effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/administered/other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.
*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.
†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence: A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

of stroke. The risk is almost linear, beginning at relatively low levels of SBP and DBP (7), and the lowering of high BP is a major factor in the impressive reduction in the stroke death rates during the last half of the 20th century and the early part of the 21st century (7,8).

The absolute risk of these adverse outcomes also increases with age. For any given SBP, the risk of fatal CAD was ≈16-fold higher for people 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 (140–159/90–99 mm Hg) accounted for nearly 60% of all excess IHD, overall cardiovascular disease (CVD), or all-cause mortality (9). Epidemiological data show that lower BP levels are associated with lower disease risks, suggesting that future coronary events can be prevented by reducing BP (10). Elevated BP represents a substantial population-attributable risk for men and women, both black and white (11,12).

1.1.1. Effects of Treatment

The risk of CVD in the patient with hypertension has been shown to be greatly reduced with effective antihypertensive therapy. Major reductions in CVD morbidity and mortality over the past 50 years have been

TABLE 2 Summary of Pharmacological Treatment of Hypertension in the Management of Ischemic Heart Disease

	ACEI or ARB	Diuretic	β-Blocker	Non-DHP CCB	DHP CCB	Nitrates	Aldosterone Antagonist	Hydralazine/ Isosorbide Dinitrate
Stable angina	1*	1†	1	2‡	2	1	2	
ACS	1*	1†	1§	2‡	2	2	2‖	
HF	1	1†	1¶			2	1‖	2

*Especially if prior myocardial infarction, left ventricular systolic dysfunction, diabetes mellitus, or proteinuric chronic kidney disease is present.
†Chlorthalidone is preferred. Loop diuretic should be used in the presence of HF (New York Heart Association class III or IV) or chronic kidney disease with glomerular filtration rate <30 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2}. Caution should be exercised in HF with preserved ejection fraction.
‡If β-blocker is contraindicated, a non-DHP CCB can be substituted, but not if left ventricular dysfunction or HF is present. Caution should be exercised if combining a non-DHP CCB with a β-blocker.
§Esmolol (intravenous) or metoprolol or bisoprolol (oral).
‖Spironolactone or eplerenone if left ventricular dysfunction, HF, or diabetes mellitus is present.
¶Carvedilol, metoprolol succinate, or bisoprolol.

ACEI indicates angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DHP, dihydropyridine; HF, heart failure; 1, drug of choice; and 2, "add-on," alternative drug, or special indications.

attributed to the increased availability and use of drug treatment for hypertension. Randomized trials have shown that BP lowering in patients with hypertension produces rapid reductions in cardiovascular risk (13) that are highly consistent with data from observational studies. For example, a 10-mm Hg lower usual SBP (or a 5-mm Hg lower usual DBP) is associated with a 50% to 60% lower risk of stroke death and an ≈40% to 50% lower risk of death resulting from CAD or other vascular causes at middle age, benefits that are only slightly smaller in older people (6). However, in one study, high blood pressure in the very elderly (>85 years) was not a risk factor for mortality, irrespective of a history of hypertension. Whereas blood pressure values below 140/70 mm Hg were associated with excess mortality (14). Likewise, there are inconsistencies across end points in the older population, with a significant association of lower BP with lower stroke deaths and HF but not with a lower rate of myocardial infarction (MI) in patients >80 years of age (15).

Several studies (Heart Outcomes Prevention Evaluation [HOPE] (16), Survival and Ventricular Enlargement [SAVE] (17), and European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease [EUROPA]) (18) have shown a beneficial effect of angiotensin-converting enzyme (ACE) inhibitors on CVD outcomes in individuals, some hypertensive and some not, but all with established CVD or at high risk for its development. However, we do not yet have 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 Trial of Preventing Hypertension (TROPHY) study (19), 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 ($p < 0.007$) 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. In addition, the treatment of prehypertension with candesartan appeared to be well tolerated, and serious adverse events occurred in 3.5% and 5.9% in patients treated with candesartan and placebo, respectively. However, the study was not designed or powered to assess CVD outcomes.

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, with a mean follow-up of 4.7 years, a target BP of <120 compared with <140 mm Hg was not associated with a reduced risk of a composite of CVD events (heart attack, a stroke, or a cardiovascular death) (20). However, the incidence of stroke was significantly less in the intensively treated group.

TABLE 3 Summary of BP Goals

BP Goal, mm Hg	Condition	Class/Level of Evidence
<140/90	CAD	IIa/B
	ACS	IIa/C
	HF	IIa/B
<130/80	CAD	IIb/B
	Post–myocardial infarction, stroke or TIA, carotid artery disease, PAD, AAA	IIb/B

AAA indicates abdominal aortic aneurysm; ACS, acute coronary syndrome; BP, blood pressure; CAD, coronary artery disease; HF, heart failure; PAD, peripheral arterial disease; and TIA, transient ischemic attack.

1.1.2. Risk Factor Interactions

Data from the Framingham Heart Study have provided evidence of a predictive role of hypertension, dyslipidemia, glucose intolerance, cigarette smoking, and left ventricular (LV) hypertrophy in CVD (21). These 5 primary risk factors are the most important modifiable determinants of CVD risk and appear to operate independently of one another. This has led to the idea that the threshold at which a patient should be treated for hypertension should be determined by a patient's burden of CVD risk factors, which in turn determine the level of CVD risk.

In the guidelines developed by the National Kidney Foundation (22), this principle has been followed for patients with albuminuria and even modest chronic renal insufficiency, for which the BP threshold for the initiation of antihypertensive therapy is 130/80 mm Hg. The American Diabetes Association has based its recommendation on age: People with diabetes mellitus should be treated to a BP of <140/80 mm Hg, except that "lower systolic targets, such as <130 mm Hg, may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden" (23). Furthermore, there is a correlation between hypertension and body mass index, with both 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 (24).

1.1.3. Risk Factor Reduction

Hypertension, dyslipidemia, diabetes mellitus, cigarette smoking, obesity, and chronic kidney disease (CKD) are independent determinants of CVD risk. Moreover, a diagnosis of peripheral artery disease (PAD) significantly increases the risk for both prevalent and incident disease in other vascular beds including the coronary and cerebral circulations (25,26). As indicated previously, hypertension represents an independent risk factor for CVD, and evidence indicates that the concomitant presence of other recognized cardiovascular risk factors results in a multiplicative increase in risk for cardiovascular events. Some current guidelines call for more aggressive BP management in the presence of other cardiovascular risk factors, and BP reduction without attention to other risk factors is inadequate to reduce cardiovascular risk. Readers should be aware that several recently published guideline documents detail the strategies for risk assessment and management. The recommendations in this document reflect the published guidelines, but readers are advised to consult other recent guidelines such as those on the assessment of cardiovascular risk (27), lifestyle management, particularly as it relates to diet and exercise (28), and the management of obesity (29) and dyslipidemia (30).

Cardiovascular risk factors may be described as nonmodifiable or modifiable. The nonmodifiable risk factors of age, sex, race/ethnicity, and genetic predisposition/family history are not addressed in this report. The potentially modifiable risk factors include dyslipidemia, diabetes mellitus, smoking, obesity, PAD, and renal insufficiency.

1.1.4. Dyslipidemia

The management of dyslipidemia was the subject of a recent ACC/AHA guideline (30).

In essence, the new guideline does not support continued use of specific low-density lipoprotein (LDL) cholesterol or non–high-density lipoprotein cholesterol treatment targets. The guideline advocates the use of a 10-year risk calculator to determine the appropriate intensity of statin therapy to reduce CVD risk in those most likely to benefit. Those patients with CVD and age ≤75 years, with LDL cholesterol ≥190 mg/dL, or with a 10-year CVD risk ≥7.5% should receive high-intensity statin therapy (e.g., atorvastatin 40–80 mg/d or rosuvastatin 20–40 mg/d to reduce LDL cholesterol by approximately ≥50%). Those with CVD who are >75 years of age or those with diabetes mellitus but with a 10-year risk of <7.5% should receive moderate-intensity statin therapy such as simvastatin 20 to 40 mg/d, atorvastatin 10 to 20 mg/d, or rosuvastatin 5 to 10 mg/d to decrease LDL cholesterol by 30% to 50%.

According to the guideline, nonstatin therapies do not provide acceptable CVD risk reduction benefits compared with their potential for adverse effects in the routine prevention of CVD.

1.1.5. Diabetes Mellitus

Type 2 diabetes mellitus is defined as a fasting plasma glucose ≥126 mg/dL, a 2-hour oral glucose tolerance test value ≥200 mg/dL, hemoglobin A_{1C} ≥6.5%, or random plasma glucose ≥200 mg/dL in a patient with classic symptoms of hyperglycemia (23). Type 2 diabetes mellitus is a strong and independent risk factor for coronary heart disease. So strong is this association that a diagnosis of diabetes mellitus could be considered a coronary heart disease risk equivalent (24), although this is controversial (31). Hypertensive patients with type 2 diabetes mellitus are also at increased risk for diabetes mellitus–specific complications, including retinopathy and nephropathy.

The pharmacological management of diabetes mellitus is beyond the scope of this review. Diabetes mellitus care is complex and requires that many issues, beyond glycemic control, be addressed.

1.1.6. Smoking

There is general consensus that smoking increases the risk of cardiovascular events. Many studies have shown a correlation between smoking and death. Life expectancy is reduced by 13.2 years in male smokers compared with nonsmokers, and this trend is stronger in female smokers, with a 14.5-year decrease in life expectancy (32). Cigarette smoking independently predicts increased risk of cardiac arrest in patients with CAD (33), and even exposure to secondhand smoke increases the risk of developing CAD by 25% to 30% (34). As with other risk factors, there is a synergistic increase in cardiovascular risk in smokers who have other, concurrent, cardiovascular risk factors. Elevated cholesterol confers a higher risk of

cardiovascular events in smokers than in nonsmokers, and smokers disproportionately tend toward unfavorable lipoprotein profiles (35). In patients with hypertension, smokers are 5 times more likely to develop severe hypertension than nonsmokers, and smokers with severe hypertension have higher mortality rates than nonsmokers (36).

It is encouraging that studies of smoking cessation demonstrate significant long-term reduction (15% over 14 years) in mortality in patients who participate in smoking cessation activities (37).

1.1.7. Obesity

The prevalence of obesity, defined as a body mass index ≥30 kg/m^2, has increased in recent years, with ≈30% of the adult US population falling into this category (38). The positive relationship between obesity and BP is well documented (39–41). Obese adults are ≈3 times more likely to be hypertensive compared with nonobese adults (40–42), and increased adiposity may explain >60% of hypertension in adults (40). Furthermore, obesity is considered a major risk factor for poor BP control in hypertensive patients (3).

Although the mechanisms of obesity-related hypertension are numerous, including activation of the sympathetic nervous system, sodium retention, activation of the renin-angiotensin-aldosterone system (RAAS), insulin resistance, and altered vascular function (43), there is no acceptable guideline on the antihypertensive drug of choice for the management of hypertension among obese patients (3,44).

Some investigators consider ACE inhibitors the drugs of choice for adequate BP control in obesity-related hypertension because of their capacity to increase insulin sensitivity and thus reduce the risk of diabetes mellitus (45). This is in contrast to thiazide diuretics, which are associated with increased risk of diabetes mellitus (46). That said, the efficacy of thiazide diuretics in lowering BP and improving cardiovascular outcomes in obese hypertensive patients is well established (47). β-Blockers also have adverse effects on glucose metabolism but have led to significant improvement in BP in obese hypertensive patients because they decrease renin activity and cardiac output, which are often elevated in obese patients (48). However, enthusiasm for the use of β-blockers as initial therapy is largely dampened by their negative profile on stroke outcomes compared with placebo and other antihypertensive drug classes (49).

There is abundant evidence in support of the effectiveness of lifestyle interventions in improving BP control among obese hypertensive patients. Recently, the AHA, ACC, and Obesity Society have published guidelines (29) for the management of overweight and obesity in adults, including identifying patients who need to lose weight, matching treatment benefits with risk profiles, diets for weight loss, lifestyle intervention and counseling, and the selection of patients for bariatric surgery.

There is also much useful information, particularly on diet and physical activity, in another AHA/ACC guidelines document on lifestyle management (28).

1.1.8. Peripheral Artery Disease

Treatment of hypertension in patients with PAD is associated with a significant reduction in the risk of MI, stroke, HF, and death. Similarly, intensive management of LDL is associated with significant reduction of cardiovascular events in patients with PAD (50). Thus, management of hypertension in patients with PAD should be based on intensive screening for and aggressive management of other concomitant cardiovascular risk factors in addition to BP reduction (3). Particularly important in this regard is the management of dyslipidemia, smoking cessation, antiplatelet therapy, diabetes mellitus management, diet, and exercise.

Currently, there is no recommended drug of choice for the treatment of hypertension in patients with PAD because clinical trials of antihypertensive drug agents such as ACE inhibitors, calcium channel blockers (CCBs), α-adrenergic blockers, and direct vasodilators have been largely unsuccessful in improving symptoms of claudication or walking distance in patients with PAD (51–53). Although β-blockers constrict resistance vessels, a meta-analysis concluded that this drug class does not worsen intermittent claudication in patients with intermittent claudication (54). Thus, β-blockers can be used in PAD patients with compelling indications for their use such as CAD or HF.

The recommendations of the ACC/AHA 2005 practice guidelines on PAD (55) include the following: 1) Antihypertensive therapy should be administered to hypertensive patients with lower-extremity PAD to achieve a goal of <140/90 mm Hg (nondiabetics) or <130/80 mm Hg (diabetics and individuals with chronic renal disease) to reduce the risk of MI, stroke, congestive HF, and cardiovascular death (Level of Evidence: A); 2) β-adrenergic blocking drugs are effective antihypertensive agents and are not contraindicated in patients with PAD (Level of Evidence: A); 3) the use of ACE inhibitors or ARBs is reasonable for patients with symptomatic (Level of Evidence: B) or asymptomatic (Level of Evidence: C) leg PAD.

1.1.9. Chronic Kidney Disease

There has been a steady increase in the prevalence of CKD, defined as kidney damage, documented by kidney biopsy or serum markers for ≥3 months, or a decrease in glomerular filtration rate to <60 mL · min^{-1} · 1.73 m^{-2} for ≥3 months (22). Kidney failure, defined as a glomerular filtration rate of <15 mL · min^{-1} · 1.73 m^{-2}, and end-stage

renal disease, which necessitates the initiation of treatment by replacement therapy (22), afflicts >525,000 patients in the United States, 65% of whom are on long-term hemodialysis (56). Hypertension represents a major independent risk factor for renal failure, with a prevalence of 28% in hypertensive patients (56). In patients with CKD, cardiovascular death is more likely than progression to end-stage renal disease, and in patients with end-stage renal disease, CVD is the leading cause of death, being 5 to 30 times higher in patients on dialysis than in the general population (57).

Even in patients with lower stages of CKD, the risk of CVD is increased independently of other risk factors, and even the smallest degree of albuminuria increases risk for CVD and all-cause death (57). In this patient population, hypertension itself is a leading cause of renal failure. BP goals in patients with CKD and microalbuminuria are lower than in the general population (22,58), with a target the same as that in patients with established CAD. Recent investigations have demonstrated that standard treatments for cardiovascular risk factors, including statin therapy, ACE inhibitors, ARBs, and antiplatelet agents, are equally effective at risk reduction in patients with CKD (who are not on dialysis) as in those without CKD and should be offered to this patient population (59). In these patients, the serum potassium concentration should be monitored frequently. Questions remain as to whether directly addressing nontraditional risk factors in patients with early evidence of renal impairment has efficacy in terms of outcomes.

1.2. Mechanisms of Hypertension and CAD

A variety of pathophysiological mechanisms contribute to the genesis of BP elevation and related target-organ damage, including CAD. These mechanisms include increased sympathetic nervous system and RAAS activity; deficiencies in the release or activity of vasodilators, for example, nitric oxide and prostacyclin, and changes in the natriuretic peptide concentration; increased expression of growth factors and inflammatory cytokines in the arterial tree; hemodynamic effects; and structural and functional abnormalities in conductance and resistance arteries, particularly increased vascular stiffness and endothelial dysfunction (60). These neurohumoral pathways interact with genetic, demographic, and environmental factors (such as heightened exposure or response to psychosocial stress, excessive dietary intake of sodium, and inadequate dietary intake of potassium and calcium) to determine whether a person will develop hypertension and related CAD. Concomitant metabolic disorders, for example, diabetes mellitus, insulin resistance, and obesity, also lead to the production of vasoactive adipocytokines that promote vasoconstriction, endothelial dysfunction, inflammation, and increased oxidative stress in the vasculature, thus increasing both BP and CVD risk (61,62). These shared pathophysiological mechanisms offer potential novel therapeutic targets for the prevention and treatment of both hypertension and CAD, with benefits that may go beyond BP lowering.

1.2.1. Genetics

Genome-wide association studies have identified multiple genetic susceptibility variants, mostly single-nucleotide polymorphisms, for atherosclerotic disease (63). It has been suggested the polymorphisms of genes of the RAAS, particularly ACE, angiotensin II receptor type 1, and angiotensinogen, are implicated in the development of CAD and MI (64,65). The presence of hypertension further increases the risk of CAD and may explain why some individuals are more predisposed than others to developing coronary events. Some polymorphisms have also been implicated in the BP response to antihypertensive treatment. For example, genetic polymorphisms coding for the matrix metalloproteinases appear to modify CVD outcomes in hypertensive patients treated with chlorthalidone, amlodipine, or lisinopril (66). These data suggest that, in the future, determination of genetic variants may be of some use for selecting appropriate antihypertensive agents to reduce both BP and the risk for CAD. However, because CAD is polygenic and its causes are multifactorial, genetic studies explain only a small proportion of the heritability of the disease (67).

1.2.2. Physical Forces and Hemodynamics

Physical forces (pressure and flow) are the primary determinants of cardiac structure and function and influence coronary arterial remodeling and atherosclerosis. When SBP is elevated, both LV output impedance and intramyocardial wall tension increase, resulting in increased myocardial oxygen demand. The wide pulse pressure and systolic hypertension in older individuals are usually attributable to inappropriately high aortic impedance, which results from decreased aortic diameter or increased effective stiffness caused by aortic wall thickening and changes in wall composition. Aging is associated with thinning and fragmentation of vascular elastin and increased collagen deposition, a degenerative process that causes increased arterial stiffness (reduction of elasticity) with an associated elevation in SBP and widening of the pulse pressure (68–70).

Increased arterial stiffness elevates SBP by increasing pulse-wave velocity and altering wave reflection from the periphery (68,71–74). With each ejection of blood from the LV, a pressure (pulse) wave is generated and travels from the heart to the periphery at a pulse-wave velocity that depends on the elastic properties of the conduit arteries. The pulse wave is reflected at any point of discontinuity

in the arterial tree and returns to the aorta and LV. The elastic properties and length of the conduit arteries determine the timing of the wave reflection (73). In younger people, the pulse-wave velocity is sufficiently slow (≈5 m/s) that the reflected wave reaches the aortic valve after closure, leading to a higher DBP and enhancing coronary perfusion by providing a "boosting" effect. In older people, particularly those who are hypertensive, pulse-wave velocity is greatly increased (≈20 m/s) because of central arterial stiffening. Thus, the reflective wave reaches the aortic valve before closure, leading to the higher SBP, pulse pressure, and afterload and a lower DBP. The increase in SBP increases cardiac metabolic requirements and predisposes to the development of LV hypertrophy and HF. Pulse pressure is closely related to SBP and is linked to CVD events, including MI and stroke. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality, fatal and nonfatal coronary events, and fatal stroke in patients with hypertension, type 2 diabetes mellitus, and end-stage renal disease (73).

1.2.3. Endothelial Dysfunction

Endothelial dysfunction, characterized by an unfavorable balance between vasodilators, for example, nitric oxide and prostaglandin E_1, and vasoconstrictors, for example, endothelin and angiotensin II, is an important contributor to BP elevation in people with vascular disease. The injured endothelium loses its vasodilator capacity and contributes to thrombosis and vascular occlusion. Release of chemotactic cytokines and adhesion molecules at the luminal surface of the injured endothelium promotes adhesion of circulating mononuclear leukocytes to the vessel wall. This low-grade, self-perpetuating vascular inflammation underlies the atherosclerotic process. Inflammatory mediators activate medial smooth muscle cells, causing them to proliferate and migrate into the subintimal space. In the presence of dyslipidemia, monocytes in 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 metalloproteinases and cathepsins, destabilizing the fibrous cap of the plaque, which may result in plaque rupture and the release of tissue factor to cause thrombosis, coronary occlusion, and acute MI.

Endothelial dysfunction and decreased nitric oxide availability related to mechanical and inflammatory injury of arteries are also associated with increased arterial stiffness and the development of isolated systolic hypertension (75). A decline in flow-mediated vasodilator capacity attributable to decreased endothelium-derived nitric oxide occurs in aging and subclinical vascular disease (76). Impaired endothelium-mediated vasodilation is responsible for the exaggerated exercise-induced increases in BP seen in these population groups (77).

1.2.4. Oxidative Stress

Oxidative stress is a critical feature of both hypertension and atherogenesis (60). In vascular tissue, the principal effectors of oxidative injury are the NAD(P)H oxidases, which are activated by mechanical forces (e.g., hypertension), hormones (particularly angiotensin II), oxidized cholesterol, and cytokines. Several NAD(P)H oxidase isoforms expressed in endothelial and vascular smooth muscle cells are upregulated in the setting of atherosclerosis and arterial injury. Angiotensin II receptor-dependent activation of NAD(P)H oxidase stimulates formation of oxidant superoxide anion (O_2^-), which reacts with nitric oxide to form the powerful oxidant peroxynitrite ($ONOO^-$). The resultant reduction in nitric oxide bioactivity contributes to the vasoconstrictor response to angiotensin II and elevates BP. Angiotensin II-induced activation of NAD(P)H oxidase also stimulates oxidation of low-density lipoprotein cholesterol and increases the expression of monocyte chemoattractant protein-1 and vascular cell adhesion molecule-1, thus linking activation of the RAAS to the atherosclerotic process.

1.2.5. Humoral and Metabolic Factors

Many of the mechanisms that initiate and maintain hypertension also damage target organs, including the coronary arteries and the myocardium. Angiotensin II elevates BP and promotes target-organ damage, including atherosclerosis, by mechanisms that include direct effects on constriction and remodeling of resistance vessels, stimulation of aldosterone synthesis and release, enhancement of sympathetic outflow from the brain, and facilitation of catecholamine release from the adrenals and peripheral sympathetic nerve terminals (1). Aldosterone can mimic or potentiate the vasotoxic properties of angiotensin II and norepinephrine. 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, cytokines, and adhesion molecules. AT1 receptor activation also contributes to endothelial damage and atherogenesis by inhibiting the mobilization of endothelial progenitor cells from the bone marrow, thus impairing endothelial regeneration and vascular repair processes (78). There is also 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.

ACE inhibitors and ARBs limit oxidative reactions in the vasculature by blocking the activation of NAD(P)H oxidase, supporting the concept that these RAAS blockers may have important vasoprotective effects beyond BP lowering (79). Furthermore, there is evidence of interaction between the RAAS and dyslipidemia: Hypercholesterolemia upregulates the RAAS, particularly vascular AT1 receptor density and functional responsiveness, and systemic angiotensin II peptide synthesis (80,81), whereas the RAAS stimulates the accumulation of low-density lipoprotein cholesterol in the arterial wall. These findings suggest that these antihypertensive drug classes may have clinically important vasoprotective effects beyond BP lowering. This hypothesis has yet to be supported by the results of randomized, controlled trials (82).

Recent evidence suggests that a second angiotensin II receptor subtype (AT2), which is not expressed in the normal vasculature but appears to be induced in the setting of vascular inflammation/hypertension/atherosclerosis, may oppose the vasoconstrictor, antinatriuretic, and proinflammatory effects of the AT1 receptor (83). Because of the apparent vasoprotective effects of AT2 receptor activation, AT2 receptor agonists have been considered for the treatment of hypertension (84), but there is no evidence that they are effective in treating hypertension in humans.

1.2.6. Calcium

Calcium ions (Ca^{2+}) are major intracellular mediators of vascular smooth muscle cell contraction and 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. In vascular smooth muscle, the voltage-gated L-type (long-acting, slowly activating) channel allows entry of sufficient Ca^{2+} for the initiation of contraction by calcium-induced intracellular Ca^{2+} release from the sarcoplasmic reticulum. Increased intracellular Ca^{2+} also has atherosclerosis-promoting effects.

The dihydropyridine CCBs bind to the α_1 subunit of the L-type channel and are highly selective for arterial/arteriolar tissues, including the coronary arteries, where they are vasodilators. 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 tissue; 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 in patients with preexisting atrioventricular nodal disease or when given with other agents, for example, β-blockers, that depress the atrioventricular node. Both CCB subclasses 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 caused by coronary spasm, for example, the Prinzmetal variant or cold-induced angina (85).

2. PREVENTION OF CARDIOVASCULAR EVENTS IN PATIENTS WITH HYPERTENSION AND CAD

2.1. Antihypertensive Drugs for the Secondary Prevention of Cardiovascular Events in Patients With CAD

Meta-analyses of antihypertensive trials have demonstrated that BP lowering is more important than the particular drug class used in the primary prevention of the complications of hypertension, including IHD. Combination antihypertensive drug therapy is typically needed to achieve and to sustain effective long-term BP control. Thus, there is no evidence to support initiating therapy with any one antihypertensive drug class over another for the primary prevention of IHD. In contrast, for secondary protection in individuals with underlying comorbid illnesses such as IHD, CKD, or recurrent stroke, not all drug classes have been proven to confer optimal or even the same level of benefit.

Whether there are class effects for antihypertensive drugs and whether each drug should be considered individually on the basis of trial results are not clearly known. It is reasonable to assume that there are class effects for thiazide and thiazide-type diuretics, ACE inhibitors, and ARBs, which have a high degree of homogeneity in both their mechanisms of action and side effects (13,86,87). There are major pharmacological differences between drugs within more heterogeneous classes of agents such as the β-blockers and CCBs (88,89). Finally, the most recent trials suggest that combining ACE inhibitors and ARBs is not beneficial for the secondary prevention of cardiovascular events (90,91), whereas combinations of renin-angiotensin blocking agents with thiazide diuretics or with CCBs show important clinical benefits (92).

2.1.1. Thiazide and Thiazide-Type Diuretics

Thiazide diuretics and the thiazide-type diuretics chlorthalidone and indapamide are highly effective in reducing BP and preventing cerebrovascular events, as demonstrated most convincingly in early studies such as the Veterans Administration studies (93), the Medical Research Council (MRC) Trial (94), the Systolic

Hypertension in the Elderly Program (SHEP) (95), and the Hypertension in the Very Elderly Trial (HYVET) (15). The benefit of chlorthalidone-based therapy in hypertension treatment is evident from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial (96). Since the publication of the results of ALLHAT, there have been concerns about whether thiazide-induced hyperglycemia and diabetes mellitus contribute to long-term IHD risk not measured during the study interval (97), but this does not seem to be the case (98–100).

2.1.2. β-Blockers

β-Blockers make up a heterogeneous class of antihypertensive drugs with differing effects on resistance vessels and on cardiac conduction and contractility. β-Blocker administration remains the standard of care in patients with angina pectoris, those who have had an MI, and those who have LV dysfunction with or without symptoms of HF unless contraindicated. The β-blockers carvedilol, metoprolol, and bisoprolol have been shown to improve outcomes in patients with HF (1).

2.1.3. ACE Inhibitors

The ACE inhibitors are effective in reducing initial IHD events and are recommended for consideration in all patients after MI. They are proven to prevent and improve both HF (101,102) and the progression of CKD (103). When combined with thiazide diuretics, ACE inhibitors reduce the incidence of recurrent stroke (104). Major trials have addressed the use of ACE inhibitors in patients with IHD but without HF or known significant LV systolic impairment.

In the HOPE study (16), 9,297 high-risk patients, of whom 80% had a history of CAD, were assigned to receive either ramipril (10 mg once nightly) or placebo and followed up for a mean of 5.0 years. 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. 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 the clinic BP with active treatment was 3/2 mm Hg. These cardiovascular benefits were initially thought to be independent of BP, but an interesting but very small HOPE substudy (105) revealed a more marked reduction in 24-hour ambulatory BP with ramipril not observed in the main trial, which reported only the clinic BPs.

In EUROPA, 12,218 patients were randomized to the ACE inhibitor perindopril or placebo (18). Although just 27% of patients were classified as hypertensive, the definition of hypertension was based on a clinic BP >160/95 mm Hg or antihypertensive therapy at baseline. The mean follow-up in EUROPA was 4.2 years. Treatment with perindopril (target dose, 8 mg daily) was associated with a 20% relative risk reduction in the composite end point 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 as the investigators defined it. The mean reduction in BP in the clinic setting was 5/2 mm Hg. At baseline, EUROPA patients were at lower cardiovascular risk than HOPE patients: One third were <55 years of age; fewer had diabetes mellitus (12% versus 39%); and proportionately more EUROPA patients took antiplatelet (92% versus 76%) and lipid-lowering (58% versus 29%) drugs.

Patients in the Prevention of Events With Angiotensin Converting Enzyme Inhibition (PEACE) trial (106) had stable CAD and normal or slightly reduced LV function and were randomized to trandolapril (target dose, 4 mg) or placebo. 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 artery revascularization. Forty-six percent of patients were hypertensive, and treatment with trandolapril was associated with a mean reduction in BP of 4.4/3.6 mm Hg. The annualized rate of all-cause mortality in PEACE was only 1.6%, a rate similar to that of an age- and sex-matched cohort without IHD. There was a relatively high use of revascularization before randomization in the PEACE trial, which may have contributed to the low event rate.

The investigators concluded that ACE inhibitors might not be necessary as routine therapy in low-risk IHD patients with preserved LV function, especially those who have received intensive treatment with revascularization and lipid-lowering agents. Thus, 2 large studies in high-cardiovascular-risk patients (HOPE and EUROPA) showed cardiovascular protective effects by ACE inhibitors, and 1 study in low-cardiovascular-risk patients (PEACE) did not.

The Ongoing Telmisartan Alone and In Combination with Ramipril Global Endpoint Trial (ONTARGET) (90) trial randomized 25,620 patients, of whom 74% had a history of CAD, to the ACE inhibitor ramipril (10 mg/d), the ARB telmisartan (80 mg/d), or the combination of these 2 drugs. After a median follow-up of 4.7 years, there was no difference in the primary outcome of cardiovascular death, nonfatal MI, nonfatal stroke, and hospitalization for HF among the 3 groups. In the combination treatment group, there was an increased risk of hypotensive symptoms, syncope, and renal dysfunction compared with those in the ramipril group. The investigators concluded that ramipril and telmisartan had similar benefits but that the combination of the ACE inhibitor and ARB in this

high-cardiovascular-risk group was associated with more side effects and no increase in benefit.

2.1.4. Angiotensin Receptor Blockers

Several ARBs have been shown to reduce the incidence or severity of IHD events, the progression of renal disease in type 2 diabetes mellitus, and cerebrovascular events. ARBs are often considered to be an alternative therapy in individuals with cardiovascular disease who are intolerant of ACE inhibitors. In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study, protection against a composite of cardiovascular events that included MI and HF was similar to that observed for the CCB amlodipine (107). However, there were important differences in BP control in the early stages of the VALUE trial (a significant BP difference in favor of amlodipine) that may have confounded outcomes for MI and especially stroke (108).

Beneficial cardiovascular outcomes were not shown in the Optimal Trial in Myocardial Infarction With the Angiotensin II Antagonist Losartan (OPTIMAAL) (109). The lack of benefit may have been attributable to inadequate doses of losartan. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), the ARB valsartan had effects similar to those of the ACE inhibitor captopril in reducing cardiovascular event end points (91). The combination of the ARB with the ACE inhibitor yielded an increase in adverse events with no incremental benefit for cardiovascular events.

In the Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSCEND) (110), 5,296 high-risk patients, of whom 75% had CAD, were randomized to telmisartan (80 mg daily) or placebo for a median duration of 4.7 years. The mean BP in the telmisartan group was 4.0/2.2 mm Hg lower than that in patients randomized to placebo. The primary outcome of cardiovascular death, nonfatal MI, nonfatal stroke, and hospitalization for HF occurred in 15.7% of the telmisartan group and 17.0% of the placebo group ($p = 0.216$). The composite of cardiovascular death, nonfatal MI, and stroke occurred in 13% of patients on telmisartan versus 14.8% of the placebo group ($p = 0.048$), and fewer patients in the telmisartan group had a cardiovascular hospitalization (30.3% versus 33%; $p = 0.025$). The tolerability of telmisartan was similar to that of placebo. The investigators concluded that telmisartan had modest benefits on the composite outcome end point of cardiovascular death, MI, and stroke and was well tolerated.

2.1.5. Aldosterone Antagonists

The aldosterone antagonists spironolactone and eplerenone lower BP alone or when added to other antihypertensive agents and have a protective effects in patients with chronic and advanced HF (in the Randomized Aldactone Evaluation Study [RALES]) (111), in patients with LV dysfunction after MI (in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study [EPHESUS]) (112), and in patients with chronic HF and mild symptoms (in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure [EMPHASIS-HF]) (113). In both RALES and EMPHASIS-HF, the majority of the subjects had IHD.

2.1.6. Calcium Channel Blockers

CCBs form a heterogeneous class of agents that lower BP but have differing effects on cardiac conduction and myocardial contractility. In ALLHAT, the primary prevention of cardiovascular events with the dihydropyridine CCB amlodipine was equivalent to that produced by the diuretic chlorthalidone or the ACE inhibitor lisinopril (96), and superiority over a β-blocker was claimed in Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) (114). Primary protection with verapamil-based therapy was shown to be similar to that of a diuretic (hydrochlorothiazide) or a β-blocker (atenolol) in the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) (115) and International Verapamil-Trandolapril Study (INVEST) (116). In the Nordic Diltiazem (NORDIL) study (117), overall cardiovascular event rates were similar for diltiazem and a combination of diuretic and β-blocker. Thus, CCBs are alternatives to β-blockers in the treatment of angina pectoris but are not recommended for secondary cardiac protection because of the relative lack of benefit of this class in preventing HF (118), particularly compared with ACE inhibitors (96) or ARBs (107).

2.1.7. Direct Renin Inhibitors

The direct renin inhibitor aliskiren lowers BP alone or when added to other antihypertensive agents but has not been shown to have protective effects in patients with CVD, including HF (119). In 2011, the Aliskiren Trial In Type 2 Diabetes Using Cardio-Renal Disease Endpoints (ALTITUDE) was stopped on the recommendation of its Data Monitoring Committee (119). ALTITUDE was comparing placebo with aliskiren 300 mg once daily added to background ACE inhibitor or ARB therapy in patients with diabetes mellitus and either increased urinary albumin excretion or both a reduced estimated glomerular filtration rate and established CVD. The primary outcome in ALTITUDE was a composite of cardiovascular death, resuscitated sudden death, nonfatal MI, nonfatal stroke, hospitalization for HF, end-stage renal disease, renal death, or doubling of baseline serum creatinine concentration, sustained for at least a month.

The basis for stopping the trial was futility for success and safety concerns, including renal dysfunction,

hyperkalemia, hypotension, and an excess of strokes. The number of patients experiencing a nonfatal stroke in the placebo group was 85 (2.0%) and in the aliskiren group was 112 (2.6%; unadjusted p = 0.04). Given prior data relating the use of antihypertensive therapy to a reduced incidence of stroke in patients with diabetes mellitus, it is possible that the imbalance in strokes represents a chance finding. Nevertheless, the general recommendation at present is to avoid the use of aliskiren in combination with another renin-angiotensin blocking agents in patients with hypertension for the primary prevention of CVD.

3. BP GOALS

3.1. Epidemiology and Coronary Physiology

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. A commonly cited target for BP is <140/90 mm Hg in general and <130/80 mm Hg in some individuals with diabetes mellitus or CKD (3,22,23). The first AHA scientific statement on the treatment of hypertension in the prevention and management of IHD also recommended a goal of <130/80 mm Hg in individuals with established CAD, with CAD equivalents, or with a Framingham Risk Score of ≥10% (1).

Some recent meta-analyses have suggested that the lower BP target for higher-risk patients is not supported by evidence from high-quality, randomized, clinical trials (120–122). Whether the lower BP goal is appropriate for the prevention of coronary disease and for the treatment of established coronary disease is the subject of intense debate. There is a historical trend for lower BP goals, especially in those with target-organ damage. Controversy remains, however, 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 (i.e., <120 mm Hg) may be appropriate to reduce myocardial workload (123). At the same time, there is a concern that excessive lowering of DBP may impair coronary perfusion. At present and despite the ACCORD study (20), discussed below, there is no consensus on the question of what the most appropriate BP target(s) should be in individuals with latent or overt CAD or prominent CAD risk factors. We believe, however, that reasonable recommendations can be developed from a synthesis of the results from relevant epidemiological studies, consideration of the theoretical issue of the J curve, data from animal studies, human studies involving surrogate end points, and randomized, clinical trials targeting different BP goals with cardiovascular events as end points.

3.1.1. Epidemiological Studies

Although epidemiological correlations cannot be used as proof of the value of treatment, they are useful in establishing expectations for reasonable treatment strategies. More specifically, epidemiological data do not necessarily predict cardiovascular outcomes when BP is lowered as a result of antihypertensive treatment. Nevertheless, population studies such as the Prospective Studies Collaboration (6), the Framingham Heart Study (124), the Women's Health Initiative (125), and the Hisayama Study (126) in Japan provide some support for a "lower is better" strategy for BP control. The debate about lower BP targets revolves around the issue of the so-called J curve and, more specifically, whether lower BP targets are appropriate or even safe for patients with CAD.

3.1.2. Coronary Perfusion, Autoregulation, and the J Curve

Many studies demonstrate that lowering SBP, DBP, or both 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 a reduction in cardiac work and an 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.

Myocardial perfusion occurs almost exclusively during diastole; therefore, DBP is the coronary perfusion pressure. Like most vascular beds, the coronary circulation is capable of autoregulation, so that a decrease 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 decrease 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 (127–129). 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 (129). 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 CAD, the hemodynamics are much more complicated. Significant CAD will shift the lower autoregulatory limit upward. However, because myocardial blood flow is very heterogeneous (130), the consequences of coronary underperfusion are unpredictable and may depend on 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 reduced 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, coronary atherosclerosis, or microangiopathy, with a reduced functional or structural capacity of coronary resistance vessels to dilate (131). This potential for impairment of myocardial oxygen supply may be compounded by an increased myocardial oxygen demand resulting from exercise, LV hypertrophy, and the increase in the output impedance of the LV caused by the increased SBP. This combination of a decreased 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. This could be translated to an upturn in the incidence of coronary events as DBP is lowered beyond this point, especially when myocardial oxygen consumption is increased such as during exercise. 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 on the DBP level that corresponds to the lower limit of autoregulation in the human coronary circulation, in healthy individuals, or in patients with hypertension and CAD. It would also be reasonable to assume 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 clinical studies with surrogate end points and the few relevant clinical trials with outcomes data to attempt to resolve this issue.

3.2. Clinical Studies

3.2.1. Lower BP With a Surrogate Outcome

An analysis of the 274 patients with CAD who completed the intravascular ultrasound substudy of the Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) trial (132) 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 (3) (<120/80 mm Hg) had a mean decrease in coronary atheroma volume of 4.6 mm^3, prehypertensive (120-139/80-89 mm Hg) subjects had no significant change, and hypertensive (≥140/90 mm Hg) subjects had a mean increase in atheroma volume of 12.0 mm^3. The authors concluded, "This study suggests that in patients with CAD, the optimal BP goal may be substantially lower than the <140/90 mm Hg level." The results of CAMELOT can be taken only as hypothesis generating because the effect of achieved BP on atheroma volume was not a prespecified outcome. Because this was a post-hoc analysis, there is the potential for residual confounding effects, especially because the individuals in the higher BP cohort were older and were more likely to have been assigned to the placebo arm of the study and therefore not treated with either amlodipine or enalapril.

3.2.2. Observational Studies and Clinical Trials

If coronary autoregulation were clinically important, it would be predicted that a U-shaped or J-shaped relationship should exist between DBP and CAD events. Furthermore, the presence of structural CAD could be expected to affect the pressure-flow relationships in the coronary arteries, with a lower tolerance of diastolic pressures. There is evidence from clinical trials 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 <90 mm Hg (133), roughly equivalent to <80 to 85 mm Hg using the more universal Korotkoff phase V. This observation was confirmed by a subsequent meta-analysis in 1987 (134) and a reanalysis of the 1985 MRC trial of mild hypertension, which reported an increased MI prevalence in those with achieved DBP <80 mm Hg (135). However, other investigators using the same data have drawn opposite conclusions about whether a J curve really exists (136,137).

A secondary analysis of data from INVEST (138,139) of patients with known CAD and hypertension showed a J-shaped relationship between BP and the primary outcome (all-cause death, nonfatal stroke, and nonfatal MI), all-cause death, and total MI, with a nadir at 119/84 mm Hg. This was not the case for stroke. These post hoc results were also cited in an analysis by Thune et al (140)

and an accompanying editorial (141) as support for the existence of a J curve and a warning against excessive lowering of BP. However, what was not mentioned was that patients in that trial who had a BP <120/70 mm Hg (the level below which the risk of adverse outcomes seemed to rise) were older and had a history of more MI, coronary artery bypass grafting or percutaneous coronary intervention, stroke or transient ischemic attack, diabetes mellitus, HF, and cancer, all confounding factors. After adjustment for these and other comorbidities, there was no increased risk down to a DBP of 50 mm Hg (139).

A different nadir for a J-shaped relationship of BP with outcome, 146.3/81.4 mm Hg, was identified in another secondary analysis, this time of the Treating to New Targets Trial (TNT) in patients with clinically evident CAD (142). The Secondary Manifestations of Arterial Disease (SMART) study of patients with manifest arteriosclerotic disease had a nadir of 143/82 mm Hg (143). The implication of these trials is that there is a higher risk of coronary events if the SBP is <146.3 or 143 mm Hg, which is clearly at odds with the mass of data from clinical trials over many decades, which show that SBPs <140 mm Hg are cardioprotective.

There are much debate and disagreement about the 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 (144–147). 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 CVD risk. Age, DBP, and cardiovascular risk are positively associated until ≈50 years of age. For the remainder of life, DBP decreases and pulse pressure widens, whereas cardiovascular risk increases exponentially. 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. However, a high SBP, a low DBP, and a wide pulse pressure are each independent risk factors for CAD, but SBP was a better predictor of outcomes than pulse pressure (5,148,149). Thus, the effects of a low DBP or wide pulse pressure cannot be separated easily from those of aging in predicting the risk of a fatal MI. This important confounder may explain much of the confusion over the existence of a J curve in observational studies.

These results suggest that wide pulse pressure is a significant determinant of whether the DBP is a major risk predictor. Therefore, in those studies that reported a J curve, possible explanations include diminished myocardial perfusion during diastole, an age-related increase in pulse pressure reflecting stiffer large arteries, or an epiphenomenon related to a known or undetected underlying illness (e.g., cancer, HF), so-called reverse causality in which the pre-existing illness explains both the low BP and the high risk of death.

There is also direct evidence against the concept of the J curve. For example, in the CAMELOT trial (150), 1,991 patients had angiographically documented CAD, 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.

3.2.3. Clinical Trials to Specifically Evaluate Lower BP Goals

Data from controlled trials designed primarily to evaluate lower BP goals in hypertensive subjects have not shown a J curve.

Population-based studies suggest that ≈45% of white adults with diabetes mellitus have coronary heart disease compared with 25% in nondiabetic individuals (151).

This makes the ACCORD study relevant to the issue of BP targets in patients with CAD. ACCORD was a trial to evaluate the overall effects of intensified glycemic control, intensive BP lowering, and reduced triglyceride levels in patients with type 2 diabetes mellitus and other risk factors for CVD. The BP study (20) randomized 4,733 patients, of whom 34% had had a previous cardiovascular event, to an intensive therapy arm, with an SBP target of <120 mm Hg, or to standard therapy, targeting an SBP of <140 mm Hg. After 1 year, the mean SBP was 119.3 mm Hg in the intensive therapy group, and 133.5 mm Hg in the standard therapy group, a difference of 14 mm Hg. During the mean follow-up of 4.7 years, there was no significant difference between the 2 groups with respect to the primary composite outcome (nonfatal MI, nonfatal stroke, or death resulting from cardiovascular causes), nonfatal MI, all-cause mortality, cardiovascular death, major coronary disease event, or fatal or nonfatal HF. However, the risk of the primary composite end point was numerically lower (by 12%) in those randomized to the lower goal. Similarly, the risk of MI was lower (by 13%) in the group randomized to the lower BP target, but this was not statistically significant. There was a putatively significantly lower incidence of stroke in the intensive therapy group (i.e., uncorrected for multiple comparisons), but the number of strokes was small (at 98). The main conclusion drawn by the investigators from this study is that an SBP <120 mm Hg in patients with type 2 diabetes mellitus is not justified (20,152). In the context of the J-curve conundrum discussed above, it is worthwhile noting that the mean achieved DBP in the intensive therapy group at 4 to 8 years after randomization was in the range of 60 to 65 mm Hg and that there was not only no significant increase in coronary events at these DBPs but in fact a

numerical decrease in such events. This finding, together with the significant protection from stroke, seen in ACCORD and most other trials could suggest a different interpretation of the ACCORD results, namely that lower DBPs are safe, at least in the range of 60 to 65 mm Hg, and may protect against stroke. The Systolic Blood Pressure Intervention Trial (SPRINT), now underway, has a trial design very similar to that of ACCORD but has enrolled only nondiabetic subjects, with a heavy representation of the elderly and patients with CKD.

3.2.4. Lower BP Goals and Diabetes Mellitus

Besides the ACCORD study, discussed above, there have been other studies relevant to secondary prevention of cardiovascular events in patients with hypertension and CAD. In a diabetic cohort of subjects with hypertension and CAD in INVEST (116), tight control of SBP (<130 mm Hg) was not associated with improved cardiovascular outcomes compared with usual control (130–139 mm Hg), although in an extended follow-up of ≈9 years, the risk of all-cause mortality was 22.8% versus 21.8%, respectively, which was just statistically significant. This is a small difference, and it is uncertain whether this can be regarded as a contribution to clinical decision making.

In the earlier Appropriate Blood Pressure Control in Diabetes (ABCD) trial, the mean BP achieved was 132/78 mm Hg in the intensive group and 138/86 mm Hg in the moderate BP control group. After 5 years, there was no difference between the groups in the progression of diabetic microvascular complications or in the rate of MI, stroke or HF. However, unlike the result in INVEST, the ABCD participants in the intensive group had a significant reduction in all-cause mortality (153).

The latest standards of medical care in diabetes mellitus (2013) (23) of the American Diabetes Association recommend a goal BP of <140/80 mm Hg; lower values, <130/80 mm Hg, "may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden."

3.2.5. Lower BP Goals for the Prevention of Stroke

Patients with atherosclerotic stroke should be included among those deemed to be at high risk (≥20% over 10 years) of further atherosclerotic cardiovascular events (154).

Besides ACCORD, in which there was no excess MI from intensive BP lowering and some benefit in preventing stroke, there have been other studies in which the effects of BP lowering on stroke outcomes have been documented. With 1 exception, the reports are consistent with supporting better stroke outcomes with BPs <130/80 mm Hg.

The exception is a post hoc observational analysis of the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) data, involving 20,330 patients with recent ischemic stroke. Hypertension was not an inclusion criterion, although most of the patients had elevated BP. PROFESS was also not a clinical trial of antihypertensive therapy but primarily of antiplatelet agents. During the 2.5 years of follow-up, the adjusted hazard ratio for subjects with an SBP in the 120- to 129-mm Hg range, compared with those in the 130- to 139-mm Hg range, was 1.10 (95% confidence interval, 0.95–1.28) for stroke and 1.01 (95% confidence interval, 0.64–1.89) for fatal stroke, both not statistically significant, and 1.16 (95% confidence interval, 1.03–1.31) for a composite end point of stroke, MI, or vascular death (155).

In a very large meta-analysis of 147 randomized trials of antihypertensive therapy (156), the percentage reductions in coronary heart disease events and stroke were similar in people with and without CVD and regardless of BP before treatment (down to 110 mm Hg SBP and 70 mm Hg DBP). A meta-regression analysis that included 31 intervention trials of BP lowering in ≈74,000 patients with diabetes mellitus reported a decrease of 13% in the risk of stroke for each 5-mm Hg reduction in SBP and of 11.5% for each 2-mm Hg reduction in DBP. In contrast, the decrease in the risk of MI approached but did not achieve statistical significance (157).

In ONTARGET, the benefits from lowering SBP to <130 mm Hg were driven mostly by a reduction in stroke. MI was unaffected and cardiovascular mortality was unchanged (90).

There is consistency in these reports, namely that intensive BP lowering to <130/80 mm Hg does not significantly decrease or increase coronary morbidity or mortality but may be protective against stroke. However, the PROFESS data are different, so the issue is still somewhat moot.

3.2.6. The Elderly

It might be predicted that a J curve would have a more devastating effect on elderly individuals, with a nadir at higher pressures, because of the greater likelihood of their having CAD and a lower coronary reserve. Very few studies have addressed this question, but those that have addressed it have produced reasonably reassuring results. An INVEST substudy (158) showed a J-shaped relationship between DBP and the primary outcome (all-cause death, nonfatal MI, or nonfatal stroke) but with a nadir of 75 mm Hg, except for the very old, for whom it was even lower at 70 mm Hg. In HYVET (15), patients >80 years of age with a mean BP of 173.0/90.8 mm Hg were randomized to receive treatment with indapamide, with perindopril added if necessary, versus placebo. In the active

treatment group, the mean BP fell by almost 30/13 mm Hg and produced a 30% reduction in stroke and a 64% reduction in HF but had no significant effect on MI. The HYVET authors stated, "The results support a target BP of 150/80 mm Hg in patients receiving treatment, since that target was reached in nearly 50% of such patients in HYVET after 2 years (15)".

With regard to the 65- to 79-year range, we take note of the recommendation of the ACC Foundation/AHA 2011 expert consensus document on hypertension in the elderly (159), which states: "The general recommended goal BP in people with uncomplicated hypertension is <140/90 mm Hg. However, this target for elderly patients with hypertension is based on expert opinion rather than on data from RCTs [randomized, controlled trials], and it is unclear whether the target SBP should be the same in 65 to 79 year old versus older patients." We have therefore retained a target of <140/90 mm Hg for this age group.

3.2.7. Conclusions

Lower SBP values may be associated with better stroke outcomes except in the case of PROFESS, and the evidence for CAD outcomes is equivocal. The evidence that excessive lowering of DBP may compromise cardiac outcomes (the J curve) is inconsistent. Epidemiological and clinical trial evidence both support and refute 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 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 even diseased coronary arteries, and no consensus exists on the minimum safe level of DBP in these individuals. Although an autoregulatory threshold has not been defined in humans, with or without CAD, it is clear, mainly from ACCORD, that lower BP targets, down to levels <120/80 mm Hg, protect against stroke and do not significantly increase CAD events. Most studies that have addressed lower BP targets have achieved DBP values in the 70- to 79-mm Hg range, which appears to be safe.

Therefore, a reasonable recommendation would be a BP target of <140/90 mm Hg for the secondary prevention of cardiovascular events in patients with CAD. However, there are some epidemiological data, several post hoc analyses of clinical trials, and a plethora of other data that support, but do not prove, that a lower target (<130/80 mm Hg) may be appropriate in some individuals with CAD. We counsel that the BP should be lowered slowly in patients with occlusive CAD with evidence of myocardial ischemia, and caution is advised in inducing decreases in DBP to <60 mm Hg, particularly if the patient is >60 years of age. 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 resulting from myocardial ischemia. In patients >80 years of age, a reasonable BP target is <150/80 mm Hg, although there are no direct data to support this, or any other specific BP goal, in this age group.

3.3. Recommendations

1. **The <140/90-mm Hg BP target is reasonable for the secondary prevention of cardiovascular events in patients with hypertension and CAD *(Class IIa; Level of Evidence: B)*.**
2. **A lower target BP (<130/80 mm Hg) may be appropriate in some individuals with CAD, previous MI, stroke or transient ischemic attack, or CAD risk equivalents (carotid artery disease, PAD, abdominal aortic aneurysm) *(Class IIb; Level of Evidence: B)*.**
3. **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 decreases in DBP to <60 mm Hg in any patient with diabetes mellitus or who is >60 years of age. 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 resulting from myocardial ischemia *(Class IIa; Level of Evidence: C)*.**

4. MANAGEMENT OF HYPERTENSION IN PATIENTS WITH CAD AND STABLE ANGINA

The 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 intake, 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 is <140/90 mm Hg (20,155,159–167).

A lower target BP (<130/80 mm Hg) may be appropriate in some individuals with CAD or those with previous MI, stroke or transient ischemic attack, or CAD risk equivalents (carotid artery disease, PAD, abdominal aortic aneurysm).

4.1. Pharmacological Therapy

4.1.1. β-Blockers

β-Blockers are the drugs of first choice for the treatment of hypertension in patients with CAD that causes angina (168,169). 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 (β_1) 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.

PAD is rarely made symptomatically worse by the use of these agents, and mild bronchospastic disease is not an absolute contraindication. Caution is needed when brittle diabetic patients with a history of hypoglycemic events are treated 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. β-Blockers should be prescribed as initial therapy for the relief of symptoms in patients with stable angina. β-Blockers may be considered as long-term therapy for all other patients with coronary or other vascular disease. Recent ACC Foundation/AHA guidelines (169,170) have recommended β-blocker therapy in patients with normal LV function after MI or ACS (Class I; Level of Evidence: B), specifically carvedilol, metoprolol succinate, or bisoprolol, in all patients with LV systolic dysfunction (ejection fraction ≤40%) or with HF or prior MI unless contraindicated (Class I; Level of Evidence: A). β-Blockers should be started and continued for 3 years in all patients with normal LV function after MI or ACS (Class I; Level of Evidence: B) (168–170).

4.1.2. Calcium Channel Blockers

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.

CCBs or long-acting nitrates should be prescribed for the relief of symptoms when β-blockers are contraindicated or cause unacceptable side effects in patients with stable angina (Class IIa; Level of Evidence: B) (168). CCBs or long-acting nitrates in combination with β-blockers should be prescribed for the relief of symptoms when initial therapy with β-blockers is unsuccessful in patients with stable angina (Class IIa; Level of Evidence: B) (168). CCBs are added to, or substituted for, β-blockers when BP remains elevated, when angina persists, or when drug side effects or contraindications mandate (171). Long-acting dihydropyridine agents are preferred over nondihydropyridines (diltiazem or verapamil) for use in combination with β-blockers to avoid excessive bradycardia or heart block. Diltiazem or verapamil should not be used in patients with HF or LV systolic dysfunction (171), and short-acting nifedipine should be avoided because it causes reflex sympathetic activation and worsening myocardial ischemia (169).

Although CCBs are useful in the management of hypertension in patients with stable 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 (116). 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. 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-type diuretic, a long-acting dihydropyridine CCB, or an ACE inhibitor (96). CAMELOT compared amlodipine or enalapril with placebo in normotensive patients with CAD, ≈60% of whom had a history of hypertension (150). Although the 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 of CAMELOT 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 (172,173).

The VALUE trial randomized 15,245 hypertensive patients at high risk of cardiac events to valsartan or

amlodipine (107). 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 resulting from 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 (174).

4.1.3. ACE Inhibitors

ACE inhibitors should be prescribed to all CAD patients with stable angina who also have hypertension, diabetes mellitus, an LV ejection fraction ≤40%, or CKD unless contraindicated (Class I; Level of Evidence: A) (169). The clinical trials that support the use of ACE inhibitors in the management of patients with stable CAD were described in the Antihypertensive Drugs for the Secondary Prevention of Cardiovascular Events in Patients With CAD section. They are the HOPE study (16), in which high-risk individuals, 80% of whom had CAD, were given an ACE inhibitor (ramipril 10 mg/d), with a reduction in CVD end points by 20% to 25%; EUROPA (18), which showed a 20% relative risk reduction in the primary end point, a composite of cardiovascular death, MI, or cardiac arrest in patients in subjects with established CAD treated with perindopril 8 mg/d versus placebo; and SAVE (17).

On the other hand, there have been negative studies. These include PEACE (106), 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. Patients in the PEACE trial were at lower risk and were receiving more aggressive secondary prevention therapy than those in the HOPE trial. In ALLHAT (96), in which 25% of participants had CAD, there were no significant differences among patients taking 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 in all-cause mortality. Soon after the ALLHAT results were published, the Second Australian National Blood Pressure Study (ANBP-2) reported the results of a prospective, open-label study in patients 65 to 84 years of age 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 (175).

4.1.4. Angiotensin Receptor Blockers

ARBs are recommended for all patients with stable angina who also have hypertension, diabetes mellitus, LV ejection fraction ≤40%, or CKD and have indications for, but are intolerant of, ACE inhibitors (Class I; Level of Evidence: A) (169). 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; Level of Evidence: B) (176). 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 (177), but the ONTARGET Study (90) failed to show additive benefit but with a substantial increase in side effects, so this combination is not recommended. In the VALUE trial (107), 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 (91), valsartan was as no more effective than captopril in patients who were at high risk for cardiovascular events after MI.

4.1.5. Diuretics

Thiazide diuretics and thiazide-like diuretics reduce cardiovascular events, as demonstrated most convincingly in early studies such as the Veterans Administration studies (93), the MRC Trial (94), and SHEP (95) and in later studies such as ALLHAT (96). These studies included subjects with CAD, and it is a reasonable assumption that diuretics are as effective in the secondary as in the primary prevention of cardiovascular events.

4.1.6. Nitrates

Long-acting nitrates or CCBs can be prescribed for the relief of symptoms when β-blockers are contraindicated or cause unacceptable side effects in patients with stable angina (Class I; Level of Evidence: B) (169). Long-acting nitrates or CCBs in combination with β-blockers should be prescribed for relief of symptoms when initial therapy with β-blockers is unsuccessful in patients with stable angina (Class I; Level of Evidence: B). Nitrates should not be used with phosphodiesterase inhibitors of the sildenafil type. Hypertension does not affect 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 generally not been shown to be of use in the management of hypertension.

4.2. 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 and thiazide-like diuretics, β-blockers (particularly after MI), CCBs, antiplatelet drugs, and drugs for the treatment of dyslipidemia. The recent ACC Foundation/AHA guidelines recommend ACE inhibitors and/or β-blockers, with the addition of drugs such as thiazide diuretics or CCBs for the management of high BP in patients with stable IHD (169).

There are no special contraindications in hypertensive patients for 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 patients with uncontrolled severe hypertension who are taking antiplatelet or anticoagulant drugs, BP should be lowered without delay to reduce the risk of hemorrhagic stroke.

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**
   b) **An ACE inhibitor or ARB if there is prior MI, LV systolic dysfunction, diabetes mellitus, or CKD; and**
   c) **A thiazide or thiazide-like diuretic *(Class I; Level of Evidence: A)*.**
2. **The combination of a β-blocker, an ACE inhibitor or ARB, and a thiazide or thiazide-like diuretic should also be considered in the absence of a prior MI, LV systolic dysfunction, diabetes mellitus, or proteinuric CKD *(Class IIa; Level of Evidence: B)*.**
3. **If β-blockers are contraindicated or produce intolerable side effects, a nondihydropyridine CCB (such as diltiazem or verapamil) may be substituted, but not if there is LV dysfunction *(Class IIa; Level of Evidence: B)*.**
4. **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 or thiazide-like 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)*.**
5. **For patients with stable angina, the BP target is <140/90 mm Hg. *(Class I; Level of Evidence: A)*. See also the previous section BP and Treatment Goals. However, a lower target BP (<130/80 mm Hg) may be considered in some individuals with CAD, with previous stroke or transient ischemic attack, or with CAD risk equivalents (carotid artery disease, PAD, abdominal aortic aneurysm) *(Class IIb; Level of Evidence: B)*.**
6. **There are no special contraindications in hypertensive patients for the use of antiplatelet or anticoagulant drugs, except that in patients with uncontrolled severe hypertension who are taking antiplatelet or anticoagulant drugs, the BP should be lowered without delay to reduce the risk of hemorrhagic stroke *(Class IIa; Level of Evidence: C)*.**

5. MANAGEMENT OF HYPERTENSION IN PATIENTS WITH ACS

Although a major risk factor for CVD, the impact of hypertension on ACS outcomes has not been well described. Few data are available on specific treatments for hypertension in patients with either STEMI or non–ST-segment–elevation ACS, including both UA and NSTEMI.

5.1. Prevalence and Impact on Prognosis

Contemporary data from the National Cardiovascular Data Registry (NCDR) Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry–Get With The Guidelines (GWTG) demonstrate a prevalence of hypertension of 65.2% among patients with STEMI and 79.2% among those with NSTEMI (ACTION Registry-GWTG 2012 first-quarter report). The prevalence of hypertension increases notably with age among ACS patients, with hypertension prevalence rates approximately double among individuals >75 versus those <45 years of age (178).

The impact of hypertension on outcomes in ACS is complex. In patients with stabilized ACS enrolled in the Sibrafiban Versus Aspirin to Yield Maximum Protection From Ischemic Heart Events Post-Acute Coronary Syndromes (SYMPHONY) trials, hypertension was an independent predictor of death and MI at 90 days (178). Moreover, hypertension is integrated into the Thrombolysis in Myocardial Infarction risk score for UA/NSTEMI as one of several classic risk factors for CAD, and the variable of ≥3 risk factors for CAD was independently associated with the composite end point of mortality and recurrent ischemic events (179). However, other multivariable risk models have not found hypertension, defined as a "yes/no" categorical variable, to be independently associated with in-hospital mortality. Indeed, lower BP more typically emerges as predictive of poor outcomes in contemporary evaluations. In both the Global Registry of Acute Coronary Events (GRACE) (180) and ACTION-GWTG (181) registries, for example,

in-hospital mortality increased by ≈20% for every 10-mm Hg decrease in BP at presentation. In contrast to the Thrombolysis in Myocardial Infarction risk score for UA/NSTEMI, in the Thrombolysis in Myocardial Infarction risk score for STEMI, SBP <100 mm Hg emerged as a powerful contributor to the model, but hypertension did not (182). In the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) and Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trials (183), a very low SBP (≤90 mm Hg) was strongly associated with 48-hour and 30-day mortality, but there was little difference in mortality between patients who had a high SBP (>140 mm Hg) and those with an SBP in the normal or prehypertensive range (121-140 mm Hg). Even severe hypertension (up to an SBP of 200 mm Hg) appeared to be protective in the NCDR ACTION analysis of ≈80,000 patients with MI (181).

Although uncontrolled hypertension does not appear to significantly increase in-hospital mortality in patients with ACS, it is a major risk factor for intracranial hemorrhage and thus remains a relative contraindication to fibrinolysis (176). When broader bleeding outcomes are evaluated across the ACS spectrum, a U-shaped association between BP and in-hospital bleeding is observed, with excess bleeding for both patients with hypertension and those with hypotension. In an analysis from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) Registry (184), bleeding rates were lowest in patients with admission SBP between 120 and 180 mm Hg and increased progressively with BPs above and below these ranges. Similarly, in the NCDR ACTION Registry Bleeding Risk Score, zero points are awarded for an SBP of 141 to 170 mm Hg on arrival, with 2 points given for SBP >200 mm Hg and 4 points for SPB ≤90 mm Hg (185). In contrast, BP variables did not emerge as independently associated with bleeding in the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) and Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trials (186).

These studies have important limitations that make it difficult to determine the impact of treating hypertension during an acute ACS episode. All of the data are observational, and it is likely that residual confounding explains some, if not most, of the observed adverse association between lower BP and mortality after ACS, particularly for BP values within or near the normal range. In addition, very limited information is available from these studies on the duration of and long-term disease burden of hypertension. Despite these limitations, the consistent associations observed between hypotension and both mortality and bleeding suggest that avoidance of hypotension should be an important treatment principle in ACS patients.

5.2. General Principles of BP Management in the Patient With ACS

The cornerstone of the management of hypertension in patients with ACS is the modification of the balance between myocardial oxygen supply and demand. Patients with ACS are especially vulnerable to perturbations in this relationship because the development of an ACS is a clinical manifestation of an alteration in the supply-demand equation such that ischemia occurs at rest or at relatively low levels of demand. 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 BP Goals section. In addition, patients with ACS often have vasomotor instability with an increased tendency to exaggerated responses to antihypertensive therapy.

Because specific trials of BP lowering have not been performed in patients with ACS, the selection of antihypertensive agents for use in the patient with ACS should be focused on selecting drugs that have an established evidence-base for risk reduction for patients with ACS independently of BP lowering. These drugs, which include β-blockers, ACE inhibitors (or ARBs), and, in selected patients, aldosterone antagonists, should typically be titrated to full doses before other agents that do not have an established evidence base are initiated.

Therapeutic targets for BP have not been established specifically for patients with ACS. Current guidelines recommend a BP target of <140/90 mm Hg and <130/80 mm Hg for patients with diabetes mellitus or CKD (1,187), but this applies more to secondary prevention than the management of hypertension in the acute phase of MI. The BP may fluctuate early after ACS; thus, efforts should focus on pain control and clinical stabilization before BP is specifically targeted. Second, the BP should be lowered slowly, and caution is advised to avoid decreases in DBP to <60 mm Hg because this may reduce coronary perfusion and worsen ischemia. A BP target of <130/80 mm Hg at the time of hospital discharge is a reasonable option. In older hypertensive individuals with wide pulse pressures, lowering SBP may lead to very low DBP values, contributing to worsening myocardial ischemia.

5.3. Specific Antihypertensive Agents in ACS

5.3.1. Nitroglycerin

Nitroglycerin has been a cornerstone of therapy for decades, and in the hypertensive patient with ACS,

nitroglycerin is effective in relieving symptoms of ischemia and pulmonary congestion and is moderately effective in lowering arterial BP. However, clinical trial evidence does not support an effect of nitrates on outcomes in ACS. 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 with STEMI 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; 7.3% versus 7.5%, respectively, in ISIS-4) (188,189). Thus, the ACC/AHA guidelines for STEMI do not recommend nitroglycerin to reduce events but only to relieve ischemic pain or acute hypertension or to manage pulmonary congestion at a Level of Evidence C. Nitrates should be used with caution in patients with inferior STEMI and are contraindicated if right ventricular infarction is present because of their effects on lowering preload. 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 (below), particularly in the convalescent stage (190).

Experience with nitrates in non-ST-segment-elevation ACS is largely extrapolated from STEMI because clinical trials in UA/NSTEMI have been relatively small. Nitroglycerin should be first administered via the sublingual route in patients with ACS, which can be followed by intravenous or topical administration of nitroglycerin or oral administration of longer-acting nitrate preparations. Patients treated with nitrates need to be monitored for potential adverse effects, in particular profound hypotension, which can exacerbate ischemia. Patients at increased risk include the elderly, individuals who are volume depleted, or those have used sildenafil within 24 hours or tadalafil within 48 hours. Nitrate tolerance is a problem even within the first 24 hours, and attempts should be made to minimize this by reducing intravenous doses and implementing intermittent dosing by non-intravenous routes once the patient is stable from an ischemic standpoint.

5.3.2. β-Blockers

β-Blockers are a cornerstone of ACS treatment because of their ability to reduce both heart rate and BP and thus myocardial oxygen demand. These agents were among the first therapies demonstrated to reduce infarct size. β-Blockers reduce early sudden death after MI both via antiarrhythmic effects and by preventing myocardial rupture. In patients with STEMI, the long-term benefits of long-term postdischarge β-blocker administration have been shown in multiple trials (191). Therefore, routine discharge use of β-blockers is now a quality performance measure for patients with ACS.

Although β-blockers should be initiated early and continued for at least 3 years after ACS (176), there has been increased attention on the appropriate selection of patients for the use of early intravenous β-blockers after ACS. Early intravenous β-blockade was shown in a number of trials performed in the fibrinolytic era to reduce either mortality or recurrent MI (192,193) and thus was used as routine therapy in ACS for many years. However, the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT)/Chinese Cardiac Study (CCC) 2 trial has led to a revision of the recommendations for intravenous β-blocker use in ACS (194). This study randomized 45,852 AMI patients at presentation to intravenous and then oral β-blockers versus placebo and assessed the coprimary outcomes of the composite of death, reinfarction, or cardiac arrest and death resulting from any cause. At discharge or up to 4 weeks, neither outcome was reduced with metoprolol. However, the COMMIT trial demonstrated 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%) with intravenous β-blocker use. The excess risk of shock was highest in the first 2 days of hospitalization, especially in patients with evidence of hemodynamic instability or borderline hemodynamics at presentation. In a subset analysis of patients with hypertension (SBP >140 mm Hg), there were no statistically 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. This important study demonstrated that early intravenous β-blocker therapy should be used selectively and restricted to patients with significant hypertension or tachycardia (i.e., caused by atrial arrhythmias), those with ongoing ischemia, and those at low risk for hemodynamic compromise.

Current ACC/AHA guidelines for STEMI and UA/NSTEMI recommend that oral β-blockade should be started within the first 24 hours, once it is established that the patient is stable and there are no contraindications (190,195). The choice of a β-blocker is based on pharmacokinetic and side-effect criteria and physician familiarity, but in general, short-acting cardioselective (β_1-selective) β-blockers without intrinsic sympathomimetic activity such as metoprolol or bisoprolol are preferable. Carvedilol, which also blocks β_2 and $\alpha_1$adrenergic receptors, has more potent BP-lowering effects than β_1-selective agents and therefore may be a good choice for patients with ACS and severe hypertension. However, it should be avoided in patients with obstructive airways disease because of the effects of β_2 antagonism on airway resistance. Contraindications to the use of β-blockers in ACS include marked first-degree heart block (ECG PR

interval >0.24 second), second- or third-degree heart block, severe bronchospastic lung disease, decompensated HF, and hypotension. Several meta-analyses concluded that cardioselective β-blockers do not produce clinically significant adverse respiratory effects in patients with chronic obstructive pulmonary disease, suggesting that β-blockers should not be withheld from these patients (196,197).

5.3.3. Calcium Channel Blockers

In general, CCBs have not been found to be useful in the setting of acute STEMI. Clinical trials of the rapid-release form of nifedipine showed an increase in mortality in patients treated with this agent after MI (198), and there is currently no role for short-acting nifedipine in clinical practice. The nondihydropyridine agents diltiazem and verapamil have also been disappointing in the early-MI setting and are not recommended for routine use in patients with STEMI (190,195).

Although several randomized, clinical trials suggested somewhat greater efficacy for CCBs in non-ST-segment-elevation ACS (199,200), some of these studies were performed ≈30 years ago and predate the era of routine β-blocker use. Moreover, benefit in these trials was limited to nonfatal recurrent ischemic events, and among patients with LV dysfunction, a detrimental effect on mortality was seen (118,201). Thus, there is no indication for routine use of CCBs in patients with UA or NSTEMI. The AHA/ACC guidelines for the management of UA and NSTEMI suggest that, in patients with continuing or frequently recurring ischemia when β-blockers are contraindicated, a nondihydropyridine CCB (verapamil or diltiazem) may be used as an alternative in the absence of severe LV dysfunction or other contraindications (195). It is prudent to avoid the use of verapamil or diltiazem in patients who have LV dysfunction, and they should not be used together with β-blockers in that situation.

Evidence for the utility of dihydropyridine CCBs in ACS is limited. These agents effectively lower BP and may relieve ischemic symptoms. All CCBs have the potential to cause hypotension, and the nondihydropyridine CCBs may precipitate conduction disturbances, particularly when used in conjunction with β-blockers.

5.3.4. ACE Inhibitors

ACE inhibitors are indicated for most patients with ACS and are a preferred option for BP management in both STEMI and non-ST elevation ACS. The data are most robust for ACE inhibitors in the STEMI population, in whom most of the trials have been performed, with results extrapolated to UA/NSTEMI.

In STEMI, ACE inhibitors reduce infarct expansion, preventing LV remodeling and chamber dilatation (202), which help to prevent downstream sequelae such as ventricular arrhythmia, HF, or even myocardial rupture. The GISSI-3, ISIS-4, and CCS-1 trials demonstrated a benefit from early administration of ACE inhibitors, with absolute reductions in mortality of 0.8%, 0.5%, and 0.5% seen as early as 4 weeks after AMI (188,189,203).

A meta-analysis from the ACE Inhibitor Myocardial Infarction Collaborative Group, which included ≈100,000 patients treated within 36 hours of acute MI, found a 7% lower relative mortality rate at 30 days in patients treated with ACE inhibitors (204). The benefit was largest in high-risk groups such as those with HF at presentation (23 lives saved per 1,000 patients) and those with an anterior MI (11 lives saved per 1,000 patients). Rates of nonfatal HF were also reduced, but hypotension and renal dysfunction were more common.

When ACE inhibitors are started later after MI among individuals with LV dysfunction and continued long term, their benefits are even more robust; mortality rates have been reduced by ≈20% to 25% in long-term trials evaluating ACE inhibitors in these high-risk subgroups (205,206).

5.3.5. Angiotensin Receptor Blockers

ARBs are a useful alternative to ACE inhibitors in patients with an ACE inhibitor contraindication or intolerance. The VALIANT trial (91) randomized patients with LV dysfunction or HF within 10 days after acute MI to additional therapy with valsartan, captopril, or the combination of the two. Valsartan was as effective as captopril for reducing cardiovascular events in these high-risk patients through 2 years of follow-up. However, combining valsartan with captopril increased the rate of adverse events without improving survival. On the other hand, OPTIMAAL showed a trend toward increased mortality in patients receiving losartan 50 mg once daily over patients receiving captopril 50 mg 3 times daily (109). These negative results may have been attributable to inadequate dosing of losartan. In summary, because of the larger and more consistent evidence base for ACE inhibitors, these agents are preferred over ARBs for patients who can tolerate them, but ARBs are a first-line alternative for ACE inhibitor-intolerant patients.

5.3.6. Aldosterone Antagonists

Aldosterone, which is incompletely suppressed even among individuals on high doses of ACE inhibitors, is thought to contribute to both adverse ventricular remodeling and myocardial fibrosis after MI. The EPHESUS trial (112) enrolled >6,600 patients with MI who had an LV ejection fraction ≤40% and either signs of HF or diabetes mellitus. Patients were randomized to the selective aldosterone inhibitor eplerenone or placebo,

initiated 3 to 14 days after MI. Eplerenone reduced total mortality by 15% and cardiovascular mortality by 17%, with a reduction in sudden cardiac death of 21%. Of those enrolled, 87% were receiving ACE inhibitors and 75% were receiving β-blockers, indicating that aldosterone antagonist therapy provides incremental benefit to these agents. Although spironolactone has not been studied specifically in ACS, this agent demonstrated a significant mortality benefit for patients with New York Heart Association (NYHA) class III or IV HF in the RALES trial (111), and it is also reasonable to use spironolactone for patients after ACS who meet EPHESUS criteria.

Aldosterone antagonists should be avoided in patients with significantly 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 the use of these agents in patients with an estimated creatinine clearance of <50 mL/min (176). Close clinical and laboratory follow-up is needed for patients receiving long-term treatment with aldosterone antagonists to mitigate the occurrence and complications of hyperkalemia (207).

Mineralocorticoid antagonists are underused among evidence-based medications after MI. This likely reflects appropriate concerns about the risk for hyperkalemia with these agents. However, many patients can safely receive these highly effective and inexpensive agents with careful follow-up.

5.3.7. Diuretics

Although thiazide and thiazide-type diuretics play a major role in the long-term control of BP, in ACS, diuretics are used primarily for patients with evidence of increased filling pressures, pulmonary venous congestion, or HF. Particular caution is needed with regard to hypokalemia, which may precipitate arrhythmias after ACS (6). Loop diuretics are preferred over thiazide and thiazide-type diuretics for patients with ACS who have HF (NYHA class III or IV) or for patients with CKD and an estimated glomerular filtration rate of <45 mL/min.

5.4. Safety of Anticoagulation in Patients With Uncontrolled Hypertension

ACS therapy includes several strategies that involve platelet inactivation and anticoagulation to reduce the risk of thrombosis and poor clinical outcomes. The relative efficacy and safety of anticoagulant and antiplatelet therapy do not differ substantially in patients with STEMI, NSTEMI, or UA. In the ACS population, these drugs are most effective when given early. These therapies can lead to major bleeding complications, most commonly in the gastrointestinal tract and at the site of femoral access for percutaneous coronary interventions. Most concerning is that, in the setting of uncontrolled hypertension, the risk of hemorrhagic stroke is increased (208). This provides another rationale for the aggressive control of hypertension in patients with ACS.

Rapidly stabilizing patients to facilitate prompt coronary reperfusion is challenging in ACS patients with severe hypertension. Inherent to the use of medications largely limiting or disrupting intraluminal thrombus formation is the potential for severe secondary bleeding. The decision to pursue an invasive as opposed to a conservative approach should be based on standard clinical, demographic, and angiographic criteria. Although hypertension per se should not influence revascularization decisions other than indirectly in relation to factors such as renal function, it should be remembered that bleeding risks are notably higher with uncontrolled hypertension.

5.5. Conclusions

Hypertension will continue to be highly prevalent among patients with ACS, particularly as the ACS population ages. The majority will respond to standard methods of hypertension control. To control BP, specific agents should be selected that have an established evidence base for risk reduction in ACS. These agents include β-blockers, ACE inhibitors or ARBs, and, in selected patients, aldosterone antagonists. Although nitrates do not change the natural history of ACS, they are very useful for hypertensive patients with ACS, particularly if there is ongoing ischemia or pulmonary congestion. Particular care should be taken to avoid hypotension, with the risk of worsening myocardial ischemia. The benefits of treating hypertension in the ACS 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 hospital.

5.6. Recommendations

1. **If there is no contraindication to the use of β-blockers, in patients with ACS, the initial therapy of hypertension should include a short-acting β_1-selective β-blocker without intrinsic sympathomimetic activity (metoprolol tartrate or bisoprolol). β-Blocker therapy should typically be initiated orally within 24 hours of presentation *(Class I; Level of Evidence: A)*. For patients with severe hypertension or ongoing ischemia, an intravenous β-blocker (esmolol) can be considered *(Class IIa; Level of Evidence: B)*. For hemodynamically unstable patients or when decompensated HF exists, the initiation of β-blocker therapy should be delayed until stabilization has been achieved *(Class I; Level of Evidence: A)*.**
2. **In patients with ACS and hypertension, nitrates should be considered to lower BP or to relieve ongoing ischemia or pulmonary congestion *(Class I; Level of Evidence: C)*. Nitrates should be avoided in patients**

with suspected right ventricular infarction and in those with hemodynamic instability. Sublingual or intravenous nitroglycerin is preferred for initial therapy and can be transitioned later to a longer-acting preparation if indicated.

3. **If there is a contraindication to the use of a β-blocker or intolerable side effects, then a nondihydropyridine CCB such as verapamil or diltiazem may be substituted for patients with ongoing ischemia, provided that LV dysfunction or HF is not present. If the angina or hypertension is not controlled on a β-blocker alone, a longer-acting dihydropyridine CCB may be added after optimal use of an ACE inhibitor *(Class IIa; Level of Evidence: B)*.**
4. **An ACE inhibitor *(Class I; Level of Evidence: A)* or an 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. For lower-risk ACS patients with preserved LV ejection fraction and no diabetes mellitus, ACE inhibitors can be considered a first-line agent for BP control *(Class IIa; Level of Evidence: A)*.**
5. **Aldosterone antagonists are indicated for patients who are already receiving β-blockers and ACE inhibitors after MI and have LV dysfunction and either HF or diabetes mellitus. 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)*.**
6. **Loop diuretics are preferred over thiazide and thiazide-type diuretics for patients with ACS who have HF (NYHA class III or IV) or for patients with CKD and an estimated glomerular filtration rate <30 mL/min. For patients with persistent hypertension not controlled with a β-blocker, an ACE inhibitor, and an aldosterone antagonist, a thiazide or thiazide-type diuretic may be added in selected patients for BP control *(Class I; Level of Evidence: B)*.**
7. **The target BP is <140/90 mm Hg in patients with ACS who are hemodynamically stable *(Class IIa; Level of Evidence: C)*. A BP target of <130/80 mm Hg at the time of hospital discharge is a reasonable option *(Class IIb; Level of Evidence: C)*. The BP should be lowered slowly, and caution is advised to avoid decreases in DBP to <60 mm Hg because this may reduce coronary perfusion and worsen ischemia.**

6. MANAGEMENT OF HYPERTENSION IN HF OF ISCHEMIC ORIGIN

Although guidelines from the ACC and the AHA exist for the treatment of chronic HF (177,209), 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) (210), ≈75% of patients hospitalized with HF had hypertension, with most having SBPs >140 mm Hg. In the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE-HF), >60% of patients seen in outpatient cardiology practices had a history of hypertension (211). Additional observational data from the Duke Databank for Cardiovascular Disease suggest a similar prevalence of hypertension in patients with ischemic cardiomyopathy (212).

6.1. Hypertension and HF

Most patients with HF have arterial hypertension (213). Not only is hypertension an important concomitant disorder, but it also contributes to the pathogenesis of both HF with reduced ejection fraction and HF with preserved ejection fraction. 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 ventricular dysfunction (214–216).

6.2. Demographics

Elevated levels of DBP and especially SBP are major risk factors for the development of HF (217,218), and long-term treatment of both systolic and diastolic hypertension has been shown to reduce the risk of HF (93,123,219). The subsequent structural abnormalities that occur in patients with hypertension, including LV hypertrophy or MI (e.g., stage B HF), portend a higher number of adverse cardiovascular outcomes. Patients presenting with HF are more likely to be older and hypertensive, and more than half have a normal LV ejection fraction (210,220). Early investigations of patients with HF such as the Framingham Heart Study cited hypertension as the most frequent comorbidity; hypertension accounted for 39% of HF cases in men and 59% in women (217). In a population-based study in Olmstead County, Minnesota, ≈50% of patients presenting with new-onset HF had hypertension (221). However, recent randomized trials have probably underestimated the contribution of hypertension to the development and progression of HF, possibly because elderly patients often are not included in clinical trials of HF. Of note, HF symptoms are rare in hypertensive individuals whose BP is well controlled at goal and who have not sustained an MI (222).

6.3. Hypertension and HF Pathophysiology

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 (223). In the second stage, CAD causes myocardial ischemia or MI, which results in HF. BP falls as HF develops, so the contribution of hypertension to the HF syndrome may be underestimated. The mechanisms by which increased LV mass leads to depressed LV ejection fraction 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 LV ejection fraction compared with 3% of those who do not, it is an important risk factor (224). However, there must be other mechanisms because increased LV mass remains associated with the development of depressed LV ejection fraction even in patients free of clinically manifest CAD, including MI. With antihypertensive treatment, the incidence of LV hypertrophy is reduced by 35%, and the development of HF is reduced by 52% (222).

The mechanisms for the progression from hypertension to clinical HF with preserved ejection fraction represent an area of ongoing investigation (225). Potential mechanisms include progressive changes in the myocardial extracellular matrix and elevation in LV filling pressures (226–231).

6.4. CAD and Acute HF

Ischemia may trigger acute pulmonary edema. The majority of patients with flash pulmonary edema have preserved systolic function (210,232–235). These patients are generally elderly and have severe CAD, typically with 1 occluded vessel and a severely stenosed coronary artery supplying collateral flow (234–236).

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 (237). In terms of management, the same principles apply when this occurs in the setting of ischemic cardiomyopathy as in ACS. Refer to the Management of Hypertension in Patients With ACS section above.

6.5. Therapeutic Strategies

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

6.6. Nonpharmacological Therapies

Sodium restriction is important in the management of both hypertension and LV dysfunction. Exercise training (238,239) has been shown to reduce recurrent cardiac events in patients with LV dysfunction resulting from ischemic causes. In the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study, exercise training was associated with modest reductions in both all-cause mortality or hospitalization and cardiovascular mortality or HF hospitalization after adjustment for highly prognostic baseline characteristics (240). Exercise training also conferred significant improvements in self-reported health status compared with usual care (241). 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 (242,243). Other nonpharmacological therapies, as discussed in the Risk Factor Reduction section, are also appropriate. These include management of dyslipidemia, diabetes mellitus, and obesity, as well as smoking cessation.

6.7. Pharmacological Therapies

When an antihypertensive regimen is devised, optimal control of BP should remain the primary goal, with the choice of drugs determined by the concomitant medical problems (e.g., CAD, diabetes mellitus, or renal disease). Ultimately, an appropriate antihypertensive regimen frequently consists of several drugs used in combination.

6.7.1. Diuretics

Diuretic-based antihypertensive therapy has repeatedly been shown to prevent HF in a wide range of target populations (244). Thiazide or thiazide-type diuretics are effective in preventing HF in hypertensive patients (222). Thiazide or thiazide-type 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. Loop diuretics such as furosemide and torsemide usually 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 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 decrease in stroke volume and activation of the RAAS and the sympathetic nervous system (245), effects that would be expected to

be harmful (246,247). 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. The Diuretic Optimization Strategies Evaluation (DOSE) trial in patients with acute HF demonstrated that a high-dose furosemide strategy was associated with a nonstatistically significant trend toward greater improvement in patients' global assessment of symptoms but no significant difference in creatinine levels. Although there were greater diuresis with the high-dose strategy and more favorable outcomes in a few secondary measures, there was also transient worsening of renal function (248).

6.7.2. ACE Inhibitors

ACE inhibitors are thought to reduce the remodeling that occurs after MI (249), to improve ischemic preconditioning (250), to reverse angiotensin II-induced vasoconstriction and inotropy, to prevent the depletion of high-energy phosphate stores, to enhance nitric oxide release through prevention of bradykinin breakdown (251), and to reduce blood coagulability through the endothelial release of tissue plasminogen activator (252). 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 (206,253). In the Acute Infarction Ramipril Efficacy (AIRE) trial (205), 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 (32.5–35 mg/d) than in those treated with a low dose of lisinopril (2.5–5 mg/d) (254). Among patients with diabetes mellitus or other cardiovascular complications (16,18), ACE inhibitors have been most notable with respect to a reduction in the onset of HF and new-onset diabetes mellitus. However, the message has not impacted clinicians as well as it should; in the IMPROVE-HF registry, only ≈80% of eligible patients with LV dysfunction were prescribed an ACE inhibitor/ARB at baseline (211).

6.7.3. Angiotensin Receptor Blockers

Compared with placebo, the ARBs losartan (255) and irbesartan (256) significantly reduced the incidence of HF in patients with type 2 diabetes mellitus and nephropathy. The VALIANT trial found valsartan to be noninferior to captopril, although it did not show superiority (61). 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 (257). The Valsartan Heart Failure Trial (Val-HeFT) assessed the efficacy of valsartan at doses up to 320 mg/d added to standard therapy for reducing morbidity and mortality in patients with HF (258). 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 (259–262). 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 (259). In the combination arm of VALIANT, valsartan and captopril together showed no increased effect over captopril alone and had a higher incidence of discontinuation because of adverse effects (91). 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 (263). The lack of superiority of the combination treatment in the VALIANT trial was likely attributable to the fact that the ACE inhibitors and ARBs were titrated aggressively at the same time in the early post-MI period, which resulted in more side effects. In 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.

6.7.4. β-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 NYHA class II to IV HF symptoms to receive metoprolol succinate versus placebo (264). 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 (265). The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial assessed patients with severe HF

symptoms who were clinically not volume overloaded and who had an LV ejection fraction <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% (266). 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 (267).

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 NYHA class III or IV HF caused by ischemic and nonischemic cardiomyopathy at a 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% (170).

Nebivolol is a β_1-selective β-blocker with vasodilating properties related to nitric oxide modulation. In the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with heart failure (SENIORS) of 2,128 patients ≥70 years of age with a history of HF, nebivolol significantly decreased all-cause mortality or cardiovascular hospital admissions over a 21-month follow-up (268).

Although all 4 of these agents (metoprolol succinate, carvedilol, bisoprolol, and nebivolol) 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 tartrate (not the formulation used in MERIT-HF, which was metoprolol succinate) (264), with mean daily doses of 42 and 85 mg/d, respectively (269). Carvedilol may be particularly appealing because of its additional α-blocking properties. There also 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. Patients should preferably receive 1 of the 4 β-blockers proven to reduce mortality (carvedilol, metoprolol succinate, bisoprolol, or nebivolol).

6.7.5. Nitrates and Hydralazine

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. The African-American Heart Failure Trial (A-heFT) (270) showed that a combination of a fixed dose of isosorbide dinitrate and hydralazine provides additional benefit in African American 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%; $p = 0.02$) (270). Therefore, for African Americans who require further BP control and relief of symptoms of HF (NYHA class III or IV), the combination of hydralazine and isosorbide is recommended together with ACE inhibitors, β-blockers, and aldosterone antagonists (271). Given the lack of randomized trial evidence to support the prevention of cardiovascular events by the use of hydralazine in the treatment of primary hypertension (272) and concerns that hydralazine may provoke angina, monotherapy with hydralazine in IHD is not recommended.

6.7.6. Aldosterone Receptor Antagonists

Aldosterone has been shown to promote myocardial fibrosis. RALES reported the effect of adding the competitive aldosterone antagonist spironolactone versus placebo to standard HF therapy in patients with stage 3 (NYHA class III or IV) HF. There was a 30% reduction in total mortality with spironolactone (111). Eplerenone, a selective aldosterone inhibitor, showed similar survival benefit in the EPHESUS trial. Patients with an LV ejection fraction 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% (112). The EMPHASIS trial supported the benefits of eplerenone in chronic HF (LV ejection fraction ≤35%) with mild symptoms (NYHA class II), in which there was a 37% reduction in the primary end point of cardiovascular death or HF hospitalization (113). 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 (112), which suggests that these agents may be particularly beneficial in patients with hypertension and HF. This class of drug is especially beneficial in patients with hypokalemia (273). Electrolytes and renal function should be monitored to prevent hyperkalemia.

6.8. Renal Denervation

The radiofrequency ablation of renal sympathetic nerves has recently gained attention for its ability to reduce BP in those with resistant hypertension (274,275). A small study has demonstrated the ability of renal denervation to induce LV hypertrophy regression and to improve LV systolic and diastolic function (276). However, in the first large-scale clinical trial of renal denervation in patents with resistant hypertension, with an appropriate control group, namely a sham procedure (Renal Denervation in Patients With Uncontrolled Hypertension

[SYMPLICITY HTN-3]) (277), there was no significant difference between the 2 groups in the reduction of SBP, which leaves the future of renal denervation in the management of hypertension uncertain. The impact of renal denervation in HF patients is also unclear, and future randomized trials are needed to clarify its role in this patient population.

6.9. Goal BP

Healthcare providers should lower both SBP and DBP in accordance with the recommendations provided in published guidelines, including the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (3). 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 (266), demonstrated benefits of carvedilol in patients with entry criteria that included SBPs down to 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. Therefore, we make the recommendation that the target BP in patients with HF should be <140/90 mm Hg, but we also suggest that consideration should be given to lowering the BP even further, to <130/80 mm Hg. Octogenarians should be checked for orthostatic changes with standing, and an SBP <130 mm Hg and a DBP <65 mm Hg should be avoided.

6.10. Drugs to Avoid

Several classes of drugs 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 (278). The dihydropyridine CCB amlodipine appeared to be safe in patients with severe systolic HF in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial (279), as was felodipine as supplementary vasodilator therapy in the Vasodilator-Heart Failure Trial (V-HeFT) III (280). Although clonidine is an effective antihypertensive agent, another drug in the same class, moxonidine, was associated with increased mortality in patients with HF (281); therefore, clonidine also should probably 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 (282). 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. Nonsteroidal anti-inflammatory drugs have been associated with increased BP accompanied by peripheral edema, weight gain, and worsening renal function, so they should be used with caution in HF patients (283,284). Studies of the direct renin inhibitor aliskiren added to ACE inhibitors or ARBs were stopped early because of concerns about increased adverse events, particularly in the setting of renal insufficiency or diabetes mellitus. Ongoing trials of aliskiren in HF with heightened safety monitoring should help define the role, if any, for this agent. Given the lack of randomized trial evidence to support the use of hydralazine without a nitrate in the treatment of primary hypertension and concerns that hydralazine may provoke angina, monotherapy with hydralazine in IHD is not recommended.

6.11. Recommendations

1. **The treatment of hypertension in patients with HF should include management of risk factors such as dyslipidemia, obesity, diabetes mellitus, smoking, and dietary sodium and a closely monitored exercise program *(Class I; Level of Evidence: C)*.**
2. **Drugs that have been shown to improve outcomes for patients with HF with reduced ejection fraction generally also lower BP. Patients should be treated with ACE inhibitors (or ARBs), β-blockers (carvedilol, metoprolol succinate, bisoprolol, or nebivolol), and aldosterone receptor antagonists *(Class I; Level of Evidence: A)*.**
3. **Thiazide or thiazide-type diuretics should be used for BP control and to reverse volume overload and associated symptoms. In patients with severe HF (NYHA class III and IV) or those with severe renal impairment (estimated glomerular filtration rate <30 mL/min), loop diuretics should be used for volume control, but they are less effective than thiazide or thiazide-type 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 with reduced ejection fraction. Either class of agents is effective in lowering BP *(Class I; Level of Evidence: A)*.**
5. **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 HF (NYHA class II–IV) with reduced ejection fraction (<40%). 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, 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 with a thiazide or thiazide-like diuretic, particularly in patients with resistant hypertension *(Class I; Level of Evidence: A)*.

6. **Hydralazine plus isosorbide dinitrate should be added to the regimen of diuretic, ACE inhibitor or ARB, and β-blocker in African American patients with NYHA class III or IV HF with reduced ejection fraction *(Class I; Level of Evidence: A)*. Others may benefit similarly, but this has not yet been tested.**
7. **In patients who have hypertension and HF with preserved ejection fraction, the recommendations are to control systolic and diastolic hypertension *(Class I; Level of Evidence: A)*, ventricular rate in the presence of atrial fibrillation *(Class I; Level of Evidence: C)*, and pulmonary congestion and peripheral edema *(Class I; Level of Evidence: C)*.**
8. **Use of β-adrenergic blocking agents, ACE inhibitors, ARBs, or CCBs in patients with HF with preserved ejection fraction and hypertension may be effective to minimize symptoms of HF *(Class IIb; Level of Evidence: C)*.**
9. **In IHD, the principles of therapy for acute hypertension with pulmonary edema are similar to those for STEMI and NSTEMI, as described above *(Class I; Level of Evidence: A)*. If the patient is hemodynamically unstable, the initiation of these therapies should be delayed until stabilization of HF has been achieved.**
10. **Drugs to avoid in patients with hypertension and HF with reduced ejection fraction are nondihydropyridine CCBs (such as verapamil and diltiazem), clonidine, moxonidine, and hydralazine without a nitrate *(Class III Harm; 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. Nonsteroidal anti-inflammatory drugs should also be used with caution in this group, given their effects on BP, volume status, and renal function *(Class IIa; Level of Evidence: B)*.**
11. **The target BP is <140/90 mm Hg, but consideration can be given to lowering the BP even further, to <130/80 mm Hg. In patients with an elevated DBP who have CAD and HF with evidence of myocardial ischemia, the BP should be lowered slowly. 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 caused by myocardial ischemia and worsening HF *(Class IIa; Level of Evidence: B)*. Octogenarians should be checked for orthostatic changes with standing, and an SBP <130 mm Hg and a DBP <65 mm Hg should be avoided.**

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*Modest.
†Significant.

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*Modest.
†Significant.

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