

## Essential Hypertension

### Part II: Treatment

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The goal of antihypertensive treatment is to reduce overall CVD risk and thus its morbidity and mortality rates. In any given patient, the decision to begin treatment is governed by the risk of CVD, which is determined by the magnitude of the BP elevation and the presence or absence of target organ disease and/or additional CVD risk factors. Recent consensus committees, including JNC VI and the World Health Organization–International Society of Hypertension (WHO-ISH) Guidelines Subcommittee, have modified traditional treatment recommendations in several important ways<sup>3,35</sup>: (1) Criteria for initiation of treatment now take into consideration total cardiovascular risk rather than BP alone, such that treatment is now recommended for persons whose BP is in the normal range but still bear a heavy burden of CVD risk factors or established CVD. (2) Systolic BP is recognized as an important target for treatment, particularly in older persons, because it is an even more important determinant of CVD risk than diastolic BP. (3) More aggressive BP goals are recommended for hypertensive patients with comorbid conditions such as diabetes mellitus or renal insufficiency. (4) The importance of tailoring the choice of antihypertensive drug treatment to the patient's individual profile of concomitant CVD risk factors/comorbid conditions is emphasized. (5) The role of simultaneous reduction of multiple CVD risk factors in improving prognosis in hypertensive patients is stressed. (6) Home and ambulatory BP measurement has been recommended because of its value in guiding therapy and enhancing adherence to treatment. (7) Greater reliance on evidence-based medicine (ie, results of randomized controlled trials with CVD outcomes) in making treatment decisions has been endorsed.

JNC VI has arrived at an empirical classification that stratifies hypertensive patients into risk groups for therapeutic decisions (Table 4). Risk group A includes patients who do not have clinical CVD, target organ damage, or other CVD risk factors. Persons with stage 1 hypertension in risk group A are candidates for a trial (up to 1 year) of vigorous lifestyle modification with BP monitoring. If goal BP is not achieved, pharmacological therapy should be added. For persons with stage 2 or 3 hypertension, immediate drug therapy is warranted. Risk group B includes patients who do not have

clinical CVD or target organ damage but do have 1 or more major CVD risk factors other than diabetes. The large majority of hypertensive patients are among this group. If multiple CVD risk factors are present, immediate drug therapy should be considered and lifestyle modification should be used as adjunctive treatment. Risk group C includes patients who have clinically manifest CVD or target organ damage. JNC VI recommends that patients who have high normal BP accompanied by renal insufficiency, heart failure, or diabetes mellitus should receive immediate pharmacological therapy accompanied by appropriate lifestyle modifications. The WHO-ISH Guidelines Subcommittee has adopted a similar scheme of risk stratification to quantify prognosis (Table 5).

The initial goal of antihypertensive therapy for most patients is to lower diastolic BP to <90 mm Hg and systolic BP to <140 mm Hg with minimal adverse effects. More aggressive BP goals ( $\leq 130/85$  mm Hg) are recommended for patients with concomitant diabetes mellitus or renal insufficiency. When self-measurement of BP or automated ambulatory BP measurements are used to guide therapy, a reasonable goal is <135/85 mm Hg.

The ultimate theoretical goal of treatment is to achieve optimal BP levels with respect to cardiovascular risk, for example, <120/80 mm Hg. The rationale for this approach is related to early reports that a major determinant of the risk reduction conferred by antihypertensive therapy is the level of BP achieved.<sup>36,37</sup> However, such aggressive BP lowering is often poorly tolerated and therefore impractical for the general hypertensive population. Furthermore, concerns have been raised that reducing diastolic BP levels to <85 mm Hg may increase the risk of ischemic events (presumably secondary to coronary hypoperfusion) in hypertensive patients with preexisting coronary artery disease and those with a pulse pressure >60 mm Hg, the so-called J-curve hypothesis. Large prospective clinical trials, particularly the recent Hypertension Optimal Treatment (HOT) study, have failed to substantiate the J-curve hypothesis.<sup>38</sup> Comparison of outcomes among the 3 randomized BP target groups in the HOT study (diastolic BP  $\leq 90$ , 85 or 80 mm Hg) was unable to detect significant differences in the risk of CVD between adjacent target groups. There was no increase in CVD risk in

This is Part II of a 2-part article. Part I of this article was published in *Circulation*. 2000;101:329–335. Note: Figures 1 and 2 and Tables 1 through 3 were published in Part I (*Circulation*. 2000;101:329–335).

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(*Circulation*. 2000;101:446–453.)

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**TABLE 4. Treatment Strategies and Risk Stratification**

BP Stage (mm Hg)	Risk Group A (No Risk Factors; No TOD/CCD)	Risk Group B (At Least 1 Risk Factor, Not Including Diabetes; No TOD/CCD)	Risk Group C (TOD/CCD and/or Diabetes, With or Without Other Risk Factors)
High normal (130–135/85–89)	Lifestyle modification	Lifestyle modification	Drug therapy Lifestyle modification
Stage 1 (140–159/90–99)	Lifestyle modification (up to 12 months)	Lifestyle modification (up to 6 months)	Drug therapy Lifestyle modification
Stages 2 and 3 (≥160/≥100)	Drug therapy Lifestyle modification	Drug therapy Lifestyle modification	Drug therapy Lifestyle modification

TOD indicates target organ damage; CCD, concomitant cardiovascular disease. From JNC VI.<sup>3</sup>

patients randomly assigned to the lowest target group (diastolic BP ≤80 mm Hg). Furthermore, data from studies of patients with isolated systolic hypertension have shown no increase in cardiovascular morbidity and mortality rates in response to reductions in diastolic BP to <90 mm Hg.

Among diabetic patients in the HOT study, there was a significantly lower risk of CVD in those assigned to the lowest BP target. Recent data support the value of lowering BP even farther in the prevention of renal disease and CVD in diabetes. For example, the results of the United Kingdom Prospective Diabetes Study Group trial demonstrated that tight BP control (an average achieved BP of 144/82 mm Hg) substantially reduced the risk of major CVD events compared with less tight BP control (an average achieved BP of 154/87 mm Hg).<sup>39</sup>

On the basis of these findings, WHO-ISH guidelines recommend achieving optimal or normal BPs in young, middle-aged, or diabetic subjects (<130/85 mm Hg; Table 1) and at least high normal BPs in elderly patients (<140/90 mm Hg; Table 1). JNC VI guidelines recommend similar BP goals, with even more aggressive targets (125/75 mm Hg) for patients with renal disease and heavy proteinuria (>1 g/24 h).

Antihypertensive treatment is indicated in isolated systolic hypertension because, especially among older persons, systolic BP is a better predictor of events (coronary heart disease,

CVD, heart failure, stroke, end-stage renal disease, and mortality from all causes) than diastolic BP. Elevated pulse pressure, an indicator of reduced compliance in large vessels, is a better marker of increased CVD risk than either systolic or diastolic BP alone, particularly in elderly individuals with isolated systolic hypertension.<sup>40,41</sup> Pharmacological therapy is well tolerated and effective in lowering BP and reducing CVD morbidity and mortality rates (particularly by reducing stroke) in patients with isolated systolic hypertension. Patients with systolic BP >160 mm Hg are generally considered to require treatment, with the goal of lowering systolic BP to <140 mm Hg, though an interim goal of systolic BP <160 mm Hg may be necessary in patients with marked elevations in pretreatment systolic BP.

**Lifestyle Modification**

**Overall Recommendations**

Lifestyle modifications are generally beneficial in reducing a variety of CVD risk factors (including high BP) and promoting good health and should therefore be used in all hypertensive patients, either as definitive treatment or as an adjunct to drug therapy.<sup>42</sup> Although sustained modifications in diet and lifestyle are difficult to achieve and have never been shown to reduce CVD morbidity or mortality rates in controlled trials, they may lower BP and obviate the need for drug treatment or

**TABLE 5. Stratification of Risk to Quantify Prognosis**

Other Risk Factors and Disease History	Blood Pressure, mm Hg		
	Grade 1 (Mild Hypertension) SBP 140–159 or DBP 90–99	Grade 2 (Moderate Hypertension) SBP 160–179 or DBP 100–109	Grade 3 (Severe Hypertension) SBP ≥180 or DBP ≥110
I No other risk factors	Low risk	Medium risk	High risk
II 1–2 risk factors	Medium risk	Medium risk	Very high risk
III 3 or more risk factors or TOD or diabetes	High risk	High risk	Very high risk
IV ACC	Very high risk	Very high risk	Very high risk

SBP indicates systolic BP; DBP, diastolic blood pressure; TOD, target organ damage; and ACC, associated clinical conditions.

From WHO-ISH.<sup>35</sup>

reduce the dosages of antihypertensive drugs needed to control BP. Therapy should be tailored to the individual characteristics of each patient, such as weight reduction and exercise for the overweight patient and moderate alcohol consumption for the heavy drinker. A reasonable generalized approach for all patients includes (1) weight loss for the overweight patient; (2) regular physical activity; (3) moderation of alcohol consumption; (4) dietary modification to reduce sodium and fat and increase calcium, potassium, magnesium, vitamins, and fiber from food sources; and (5) cessation of smoking. Such an approach has been shown to produce significant sustained reductions in BP while reducing overall cardiovascular risk. In well-motivated patients with stage 1 or 2 hypertension, modifying lifestyle effectively lowers BP and may be more important than the initial choice of antihypertensive drug. The same lifestyle modifications that are effective in treating hypertensive patients may be useful in the primary prevention of essential hypertension.

### **Weight Reduction**

Weight loss is closely correlated with reduction in BP and appears to be the most effective of all nonpharmacological measures used to treat hypertension. Weight loss also enhances the efficacy of antihypertensive drugs. This effect is independent of dietary sodium restriction and is seen in both obese and nonobese hypertensive individuals. Weight reduction of as little as 10 lb reduces BP in a large proportion of overweight hypertensive persons and has a beneficial effect on associated coronary artery disease risk factors such as insulin resistance, diabetes, hyperlipidemia, and left ventricular hypertrophy, as well as the patient's self-image and sense of well-being.

Weight reduction of at least 10 lb (with further increments depending on the initial response and the patient's baseline weight) through a combination of dietary caloric restriction and increased physical activity is recommended for all overweight hypertensive individuals.<sup>35</sup> These patients should avoid appetite suppressants, which contain sympathomimetics such as phenylpropranolamine that can elevate BP. The appetite suppressant drugs fenfluramine and phentermine have been withdrawn from the market because of cardiovascular toxicity, including serious mitral, aortic, and tricuspid regurgitant lesions and, rarely, pulmonary hypertension. Because sustained weight reduction is so difficult to achieve, more emphasis should be placed on prevention of weight gain, particularly in younger individuals with high normal BP and in families with a high prevalence of hypertension.

### **Increased Physical Activity**

At least 30 minutes of moderately intense physical activity, such as brisk walking, swimming, bicycling, or yard work, at least 3 times per week (preferably once per day) can lower BP in both normotensive and hypertensive individuals. Studies suggest that such moderate activity may lower systolic BP by  $\approx$ 4 to 8 mm Hg and is more effective than more strenuous forms of exercise such as running and jogging.<sup>43</sup> Additional benefits of regular physical activity include weight loss, enhanced sense of well-being, improved functional health

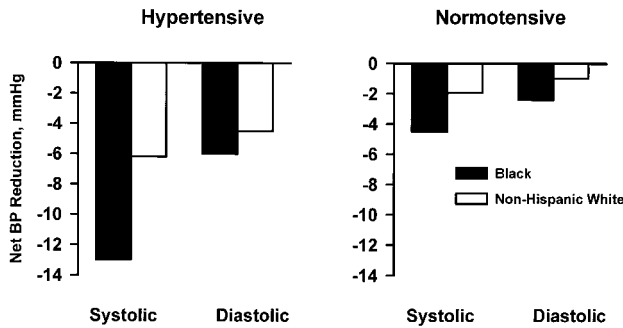
status, and reduced risk of CVD and mortality from all causes. Accordingly, regular aerobic physical activity is recommended for all hypertensive individuals, including those with target organ damage. Patients with advanced or unstable CVD may require a medical evaluation before initiation of exercise or a medically supervised exercise program. Isometric exercise such as heavy weight lifting can have a pressor effect and should be avoided.

### **Moderation of Alcohol Intake**

Alcohol consumption elevates BP both acutely and chronically. In cross-sectional and prospective studies involving all kinds of populations, the relationship between alcohol consumption, BP levels, and the prevalence of hypertension has been remarkably consistent.<sup>8</sup> The relationship is linear, but some studies show a threshold effect of 2 to 3 drinks a day. The effect increases with age, is independent of the type of alcoholic beverage, and is additive but independent of the effects of obesity, oral contraceptives, and high salt intake.<sup>44</sup> Clinical studies show that BP falls 4 to 5 mm Hg in days or weeks with abstinence from alcohol.<sup>45</sup> However, moderate alcohol consumption ( $<$ 3 standard drinks a day) reduces overall CVD risk in the general population.<sup>46</sup> Whether this risk reduction also occurs in the hypertensive population needs to be studied further. Those having more than 2 standard alcohol drinks per day show an increase in both mortality rates and hypertension.<sup>47</sup> It is estimated that in men, the contribution of alcohol to the prevalence of hypertension is 11%.<sup>47</sup> In nonobese heavy drinkers, systolic BP was  $\approx$ 4 to 5 mm Hg higher than in nondrinkers.<sup>44</sup> The mechanism by which alcohol raises BP is not known. Excessive alcohol intake also appears to cause resistance to antihypertensive therapy. For unrelated health reasons, alcohol consumption is not recommended for nondrinkers; for drinkers, intake should be limited to 1 oz of alcohol per day (2 oz of 100-proof whiskey, 8 oz of wine, or 24 oz of beer) in most men and half that amount in women and small men.

### **Dietary Modification**

Two clinical trials, one with a comprehensive food plan that supplied the recommended dietary allowances of all major nutrients<sup>48</sup> and the other with a diet rich in fruits, vegetables, and low-fat dairy products and reduced in saturated and total fat,<sup>9,49</sup> produced reductions in BP comparable to or greater than those usually seen with monotherapy for stage 1 hypertension. The Dietary Approaches to Stop Hypertension (DASH) trial showed overall reductions in BP of 11.4/5.5 mm Hg in hypertensive persons on a diet rich in fruits, vegetables, and low-fat dairy products, compared with control subjects on a so-called "usual American diet," while dietary sodium intake and weight were held constant. The DASH "combination diet" also produced reductions in BP of 3.5/2.1 mm Hg in subjects without hypertension. Remarkably, subgroup analysis of the DASH trial indicated that the combination diet lowered BP effectively in all participating groups examined, independent of race, sex, age, BMI, level of education, income, physical activity, family history of hypertension, and geographic location of the study site.<sup>49</sup> African American participants, who were intentionally overrepresent-



**Figure 3.** Joint effect of race and hypertension status on BP response to DASH combination diet.

ed in the trial (60% of the cohort), realized greater benefit from the DASH combination diet (mean BP decrease 6.9/3.7 mm Hg;  $P < 0.001$ ) than whites (mean BP decrease 3.7/2.4 mm Hg;  $P < 0.01$ ). Among African Americans with hypertension, the DASH combination diet reduced BP by 13.2/6.1 mm Hg and among normotensive African Americans by 4.3/2.6 mm Hg (Figure 3). Among whites, BP decreased by 6.3/4.4 mm Hg in hypertensive participants and 2.0/1.2 mm Hg in normotensive participants.

The success of the DASH diet in lowering BP cannot be attributed solely to its micronutrient content (high in calcium, potassium, and magnesium) because the foods included in the DASH trial contain complex combinations of minerals, macronutrients, fiber, phytochemicals, vitamins, and other factors that alone or in combination could lower BP.<sup>50</sup> Translation of the results of the DASH trial to advice for the general public or the universe of hypertensive patients is more easily accomplished by recommending 4 servings of fruit, 4 servings of vegetables, and 3 servings of low-fat dairy products per day than by prescribing a specific daily intake of calcium, potassium, and magnesium. The paradigm shift toward recognition of the powerful role of total diet (rather than individual nutrients) in the prevention and treatment of hypertension in particular and CVD in general deserves emphasis.

### Sodium Reduction

High sodium intake has generally been related to BP elevation, particularly in hypertensive individuals, and this effect appears to be augmented by concomitant low potassium intake. On the basis of these observations and the small but consistent BP-lowering effects observed in clinical trials of dietary sodium reduction in hypertensive subjects, particularly obese patients, older patients, blacks, and women, avoiding excessive sodium intake is recommended for all hypertensive individuals. Additional benefits of sodium reduction include reduced diuretic-induced hypokalemia and greater ease of BP control with diuretic therapy, protection from osteoporosis and fractures by reducing urinary calcium excretion, and favorable effects on left ventricular hypertrophy. A number of agencies have codified this recommendation as a reduction in daily consumption of sodium chloride to  $\leq 6$  g and of sodium to  $\leq 2400$  mg.<sup>3,35,51,52</sup> This can be achieved by avoiding obviously salty foods, not adding salt at the table, and eating more meals cooked directly from natural

ingredients. Whether this level of sodium reduction is helpful for the general population in preventing hypertension and related CVD morbidity and mortality is a matter of debate, considering the minimal effect of dietary sodium reduction on BP in normotensive subjects and possible adverse effects of reduced sodium intake on the cardiovascular system over time.<sup>53,54</sup> Furthermore, the impressive results of the DASH diet (which is rich in fruits, vegetables, and low-fat dairy foods) in lowering BP in hypertensive subjects may diminish the role of modifying intake of single nutrients, including sodium, in hypertension control and prevention.

### Potassium Repletion

Maintenance of adequate potassium intake ( $>100$  mmol/d), preferably from dietary sources, is recommended for hypertensive individuals and those with high normal BP. A diet rich in fruits and vegetables (DASH diet) is better than pills or other supplements as a source of potassium because these foods contain other nutrients, for example, calcium, magnesium, and vitamins, which may also have beneficial effects on BP. Moreover, it is clear that potassium supplements can be harmful and should be avoided or used only with extreme caution in patients with renal insufficiency, diabetics, and those receiving potassium-sparing diuretics, ACE inhibitors, or angiotensin II receptor blockers.<sup>55</sup>

### Calcium Repletion

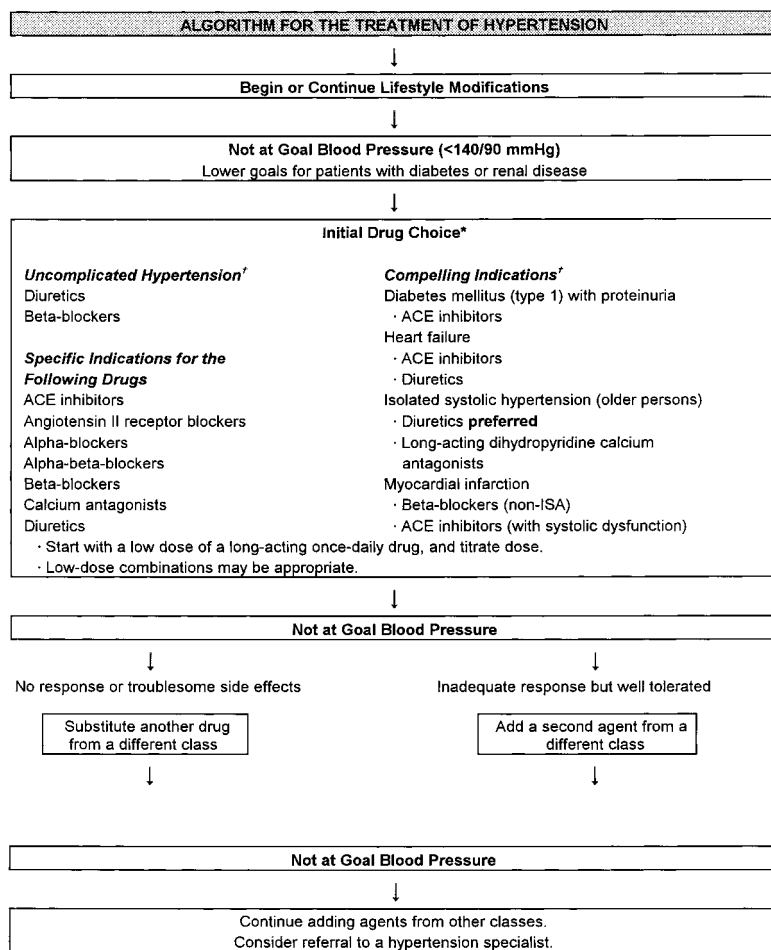
Although there is insufficient evidence to recommend high calcium intake for prevention or treatment of hypertension, calcium deficiency should be avoided. Importantly, 75% to 90% of adults in the United States fail to consume the recommended daily allowance of calcium (1200 to 1500 mg for adolescents/young adults and pregnant/nursing women; 1000 mg for mature adults younger than 65 years of age; 1500 mg for adults older than 65 years of age). Inadequate calcium intake is particularly common in populations at high risk of developing hypertension, including the elderly and African Americans. Maintaining the recommended daily allowance for calcium, preferably from food sources, is beneficial for a variety of reasons, such as preventing osteoporosis. Furthermore, the DASH trial showed that a diet rich in low-fat dairy foods is associated with major reductions in BP in both normotensive and hypertensive persons.<sup>9,48–50</sup>

### Macronutrient Alteration

A variety of macronutrients, including fiber, fish oils rich in  $\omega$ -3 fatty acids, garlic, fat, carbohydrates, and protein have been related to BP, mainly on the basis of observations that populations that consume unusually large amounts of these nutrients have low BP and a low prevalence of hypertension. Careful observational studies in this area are few and have tended not to confirm the hypothesized relationships between macronutrient intake and BP. Similarly, clinical trial data are sparse. Further study is needed before a judgment can be made regarding the value of these interventions in the prevention or treatment of hypertension.

### Smoking Avoidance/Cessation

Although cessation of smoking does not alter BP, it is important for the prevention of both CVD and non-CVD



**Figure 4.** Algorithm for the treatment of hypertension. From JNC VI.<sup>3</sup>

\* Unless contraindicated. ACE indicates angiotensin-covering enzyme; ISA, intrinsic sympathomimetic activity  
<sup>f</sup> Based on randomized controlled trials.

morbidity and mortality. All hypertensive patients who smoke should be counseled to stop, and nicotine replacement therapy should be considered. Measures to avoid or minimize weight gain after one stops smoking may be needed.

## Pharmacological Treatment

### General Considerations

Reducing BP by pharmacological means clearly reduces CVD morbidity and mortality rates. Benefits include protection from stroke, coronary events, heart failure, progression of renal disease, progression to more severe hypertension, and, most importantly, mortality from all causes. The benefits of antihypertensive treatment in the elderly and in persons with isolated systolic hypertension are greater than in younger persons. However, keeping patients on treatment and treating to a goal BP are difficult in practice, and <25% of hypertensive patients in the United States are controlled (BP <140/90 mm Hg).<sup>3,56</sup> A major problem is the very high rate of discontinuance or change in medications by hypertensive patients: 50% to 70% of new treatments are changed or discontinued within the first 6 months in most practices.<sup>42</sup> These high discontinuance rates probably reflect a combination of adverse drug effects, cost of drugs, poor efficacy, changes in provider, dissatisfaction with other aspects of care, and lack of understanding of the risks of target organ damage.

Dealing with these barriers to adherence to prescribed therapy is the key to the successful treatment of hypertensive patients. Maximizing adherence is clearly more important than choosing a specific drug or regimen in achieving the desired outcome.

Given these practical considerations, it is reasonable to individualize antihypertensive treatment on the basis of each patient's personal needs with respect to tolerability, convenience, and quality of life. Initiation of treatment with a drug that is expected to be well tolerated and therefore likely to be effective in lowering BP over time is prudent. Long-acting agents are preferable because adherence to therapy and consistency of BP control are superior when the drug is taken once a day. Low-dose, fixed-dose combination therapy can be used in place of monotherapy as initial treatment or as an alternative to adding a second agent of a different therapeutic class to unsuccessful monotherapy. The advantage of this approach is that low doses of drugs that act by different mechanisms may have additive or synergistic effects on BP with minimal dose-dependent adverse effects. Giving the patient a single tablet provides an additional benefit.

The treatment algorithm outlined in Figure 4 has been put forth by JNC VI. Treatment should always include lifestyle modifications. For the minority of hypertensive patients without comorbid conditions, target organ damage, or con-

**TABLE 6. Antihypertensive Drug Therapy for Patients With Comorbid Conditions**

Indication	Drug Therapy
Compelling indications unless contraindicated	
Diabetes mellitus (type 1) with proteinuria	ACE inhibitors
Heart failure	ACE inhibitors, diuretics, $\beta$ -blockers
Isolated systolic hypertension (older patients)	Diuretics (preferred), calcium channel blockers (long-acting dihydropyridine)
Myocardial infarction	$\beta$ -Blockers (non-intrinsic sympathomimetic activity), ACE inhibitors (with systolic dysfunction)
May have favorable effects on comorbid conditions	
Angina	$\beta$ -Blockers, calcium channel blockers (long-acting)
Atrial tachycardia and fibrillation	$\beta$ -Blockers, calcium channel blockers (non-dihydropyridine)
Cyclosporine-induced hypertension	Calcium channel blockers
Diabetes mellitus (type 1 and 2) with proteinuria	ACE inhibitors (preferred), calcium channel blockers
Dyslipidemia	$\alpha$ -Blockers
Essential tremor	$\beta$ -Blockers (noncardioselective)
Heart failure	$\beta$ -Blockers, angiotensin II receptor blockers, spironolactone
Hyperthyroidism	$\beta$ -Blockers
Migraine	$\beta$ -Blockers (noncardioselective), calcium channel blockers (non-dihydropyridine)
Myocardial infarction	Diltiazem, verapamil
Osteoporosis	Thiazides
Benign prostatic hyperplasia	$\alpha$ -Blockers
Renal insufficiency (except in renovascular hypertension and creatinine $\geq$ 265.2 mmol/L [3 mg/dL])	ACE inhibitors
Unfavorable effects on comorbid conditions	
Bronchospastic disease	$\beta$ -Blockers
Depression	$\beta$ -Blockers, central $\alpha$ -antagonists, reserpine
Diabetes mellitus (types 1 and 2)	$\beta$ -Blockers, high-dose diuretics
Dyslipidemia	$\beta$ -Blockers (nonintrinsic sympathomimetic activity), diuretics (high dose)
Gout	Diuretics
2° and 3° heart blockers	$\beta$ -Blockers, diltiazem, verapamil
Heart failure	Calcium channel blockers (except amlodipine, felodipine)
Liver disease	Labetalol, methyldopa
Peripheral vascular disease	$\beta$ -Blockers
Pregnancy	ACE inhibitors, angiotensin II receptor blockers
Renal insufficiency	Potassium-sparing agents
Renovascular disease	ACE inhibitors, angiotensin II receptor blockers

Modified from JNC VI.<sup>3</sup>

comitant CVD risk factors, JNC VI recommends starting drug therapy with a diuretic or  $\beta$ -blocker because (1) these are the only antihypertensive drugs shown to reduce CVD morbidity and mortality rates in randomized controlled trials, and (2) they are less costly than the newer classes of drugs. Long-term, controlled clinical trials are needed to clarify the benefits and risks of CVD outcomes associated with BP reduction with the newer classes of antihypertensive agents, particularly in patients with multiple CVD risk factors. Randomized trials in progress around the world, with a projected patient enrollment of 200 000, are addressing this issue. These randomized trials, which are free of treatment assignment bias, are needed to settle controversies raised by uncontrolled observational studies about the potential adverse effects of some classes of antihypertensive drugs on CVD outcomes, such as the recent calcium channel blocker controversy. Three to 5 years of follow-up will be required to

determine whether there are significant differences in CVD outcomes in response to treatment with different classes of antihypertensive drugs.

### Comorbid Conditions

Comorbid conditions that influence the choice of antihypertensive therapy, principally target organ damage and major CVD risk factors, have been demonstrated in 50% to 70% of patients with essential hypertension, particularly the elderly (Table 6). Antihypertensive drugs that have added benefit for patients with these conditions should be included as part of the treatment program, although additional drugs may be needed to bring BP under control. Agents that have adverse effects on these comorbid conditions should not be selected as first- or second-line therapy but may be needed to control BP in patients with resistant hypertension who also have one of these comorbid conditions.

Compelling indications for initial drug choices from specific classes are based on randomized clinical trials. ACE inhibitors, used alone or in combination with diuretics and digoxin, both prevent congestive heart failure and reduce morbid and mortal events in patients with established failure and therefore are recommended as first-line agents for treating hypertensive patients with this condition. Recent clinical trials have also shown benefit from appropriately dosed  $\beta$ -blockers in the setting of heart failure.<sup>57,58</sup> Clinical trials in progress are focused on the question of whether angiotensin II receptor blockers (ARBs) will prove useful in the treatment of heart failure, either in substitution for or as an adjunct to ACE inhibitors. Alternative therapies include hydralazine and isosorbide dinitrate as well as the dihydropyridine calcium channel blockers amlodipine and felodipine, which have been shown to be safe in patients with heart failure.

ACE inhibitors are recommended as first-line agents for treating hypertension in diabetic patients, particularly patients with type 1 diabetes and/or diabetic nephropathy, because they reduce proteinuria and slow the rate of deterioration in renal function. Ongoing clinical trials are testing whether ARBs have similar benefits. Other classes of antihypertensive drugs can be used and indeed are needed in diabetics. Because of the aggressive nature of target organ damage in diabetics, a lower BP goal (<130/85 mm Hg) is recommended, usually necessitating a multidrug regimen.

Hypertensive patients with renal dysfunction should be evaluated thoroughly to rule out reversible causes of hypertension and/or end-stage renal failure. These patients should be treated aggressively (goal BP <130/85 or  $\leq$ 125/75 mm Hg) in the presence of proteinuria (>1 g/24 h) to prevent both progression of renal disease and CVD events. As in diabetes (which often accompanies hypertension in these patients), multidrug therapy is usually needed to accomplish this goal. An ACE inhibitor should be included in the regimen unless contraindicated. Loop diuretics are needed for BP control in patients with serum creatinine levels  $\geq$ 2.5 mg/dL. Potassium-sparing diuretics should be avoided.

Patients with coronary heart disease clearly have target organ damage and deserve aggressive antihypertensive treatment. However, they are exceptionally vulnerable to rapid fluctuations in BP, which may be associated with catecholamine surges and concomitant arrhythmias and myocardial ischemia/infarction. Short-acting drugs that cover the hours after waking, the peak time for CVD events, are clearly preferable in coronary patients.  $\beta$ -Blockers and some long-acting calcium channel blockers have antiangina properties, whereas  $\beta$ -blockers are useful in the secondary prevention of acute myocardial infarction and sudden cardiac death. In randomized controlled trials, ACE inhibitors have been shown to prevent myocardial remodeling, heart failure, and death in patients with myocardial infarction and left ventricular systolic dysfunction.  $\beta$ -Blockers and more recently spironolactone have also been shown to decrease morbidity and mortality rates in patients with heart failure.<sup>57,59</sup> The utility of ARBs in these patients is currently being tested in clinical trials.

## Conclusions

Recognition of the genetic and environmental factors that elevate BP and lead to target organ damage and death from CVD may pave the way for nonpharmacological methods of prevention, treatment, and even cure of hypertension. There is now clear evidence that changes in lifestyle, including dietary modifications that reduce body weight, fat, and alcohol intake and increase potassium and calcium intake, as well as exercise, can reduce or normalize BP in many people. Identification of the constellation of genes responsible for inherited essential hypertension will likely yield even more targeted and effective preventive and therapeutic strategies. This may occur through specific lifestyle modifications directed toward persons at high risk for CVD because of their genotype, made possible by more selective, genotype-targeted "pharmacogenomic" treatments or even gene therapy.

Results of controlled clinical trials and observational studies have led to important modifications in traditional guidelines for antihypertensive treatment. The threshold for initiating treatment is now based on total risk for CVD rather than BP alone. Treatment is now recommended for those persons with high normal BP who have multiple CVD risk factors or established CVD. Simultaneous reduction of multiple CVD risk factors rather than isolated treatment of hypertension is now recommended, as is tailoring the choice of antihypertensive treatment to the patient's unique profile of concomitant CVD risk factors and/or comorbid conditions. Systolic BP has emerged as an important therapeutic target because it is a more important determinant of CVD risk than diastolic BP. Home and ambulatory BP measurement is recommended for its value in guiding therapy and enhancing adherence to treatment. More aggressive BP goals are appropriate for hypertensive patients with comorbid conditions such as diabetes and renal insufficiency, and greater reliance on evidence-based medicine in making treatment decisions has been endorsed. Implementation of these contemporary treatment recommendations, coupled with future advances that will accompany our more complete understanding of the pathophysiology of hypertension, holds the promise for improved BP control and prevention of CVD in the general population.

## Acknowledgments

This work was supported by National Institutes of Health grant HL-28982.

## References

- Note: References 1 through 34 appear in Part I of this article, which was published in *Circulation*. 2000;101:329–335.
35. World Health Organization–International Society of Hypertension guidelines for the management of hypertension. Guidelines Subcommittee. *J Hypertens*. 1999;17:151–183.
  36. Isles CG, Walker LM, Beevers GD, Brown I, Cameron HL, Clarke J, Hawthorne V, Hole D, Lever AF, Robertson JW, Wapshaw JA. Mortality in patients of the Glasgow Blood Pressure Clinic. *J Hypertens*. 1986;4:141–156.
  37. Lindholm L, Ejlertsson G, Schersten B. High risk of cerebrocardiovascular morbidity in well treated male hypertensives: a retrospective study of 40–59-year-old hypertensives in a Swedish primary care district. *Acta Med Scand*. 1984;216:251–259.

38. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet*. 1998;351:1755-1762.
39. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ*. 1998;317:703-713.
40. Psaty BM, Furberg CD, Kuller LH, Borhani NO, Rautaharju PM, O'Leary DH, Bild DE, Robbins J, Fried LP, Reid C. Isolated systolic hypertension and subclinical cardiovascular disease in the elderly: initial findings from the Cardiovascular Health Study. *JAMA*. 1992;269:214-215.
41. Mitchell GF, Moye LA, Braunwald E, Rouleau JL, Bernstein V, Geltman EM, Flaker GC, Pfeffer MA. Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. *Circulation*. 1997;96:4254-4260.
42. Oparil S. High blood pressure. In: Goldman L, Bennett JC, eds. *Cecil Textbook of Medicine: 21st Century Edition*. Philadelphia, Pa: WB Saunders; 1999.
43. Puddey IB, Cox K. Exercise lowers blood pressure—sometimes? Or did Pheidippides have hypertension? *J Hypertens*. 1995;13:1229-1233. Editorial.
44. Arkwright PD, Beilin LJ, Rouse I, Armstrong BK, Vandongen R. Effects of alcohol use and other aspects of lifestyle on blood pressure levels and prevalence of hypertension in a working population. *Circulation*. 1982;66:60-66.
45. Beilin LJ, Puddey IB, Burke V. Alcohol and hypertension: kill or cure? *J Hum Hypertens*. 1996;10(suppl 2):S1-S5.
46. Puddey IB, Beilin LJ, Rakic V. Alcohol, hypertension and the cardiovascular system: a critical appraisal. *Addict Biol*. 1997;2:159-170.
47. MacMahon S. Alcohol consumption and hypertension. *Hypertension*. 1987;9:111-121.
48. McCarron DA, Oparil S, Chait A, Haynes RB, Kris-Etherton P, Stern JS, Resnick LM, Clark S, Morris CD, Hatton DC, Metz JA, McMahon M, Holcomb S, Snyder GW, Pi-Sunyer FX. Nutritional management of cardiovascular risk factors: a randomized clinical trial. *Arch Intern Med*. 1997;157:169-177.
49. Svetkey LP, Simons-Morton D, Vollmer WM, Appel LJ, Conlin PR, Ryan DH, Ard J, Kennedy BM, for the DASH Research Group. Effects of dietary patterns on blood pressure: subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomized clinical trial. *Arch Intern Med*. 1999;159:285-293.
50. Moore TJ, Appel LJ, Bray GA, Svetkey LP, Vollmer WM. More salt, please: the DASH Steering Committee. *Science*. 1998;282:1049-1051. Letter.
51. Oparil S, Calhoun DA. High blood pressure. *Sci Am Med*. 1997;1:1-14.
52. Kotchen TA, McCarron DA, for the Nutrition Group. Dietary electrolytes and blood pressure. *Circulation*. 1998;98:613-617.
53. Alderman MH, Madhavan S, Cohen H, Sealey JE, Laragh JH. Low urinary sodium is associated with greater risk of myocardial infarction among treated hypertensive men. *Hypertension*. 1995;25:1144-1152.
54. Alderman MH, Cohen H, Madhavan S. Dietary sodium intake and mortality: the National Health and Nutrition Examination Survey (NHANES I). *Lancet*. 1998;351:781-785.
55. Kassirer JP, Harrington JT. Fending off the potassium pushers. *N Engl J Med*. 1985;312:785-787. Editorial.
56. Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, Horan MJ, Labarthe D. Prevalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension*. 1995;25:305-313.
57. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure: US Carvedilol Heart Failure Study Group. *N Engl J Med*. 1996;334:1349-1355.
58. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353:2001-2007.
59. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J, for the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341:709-717.

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KEY WORDS: hypertension ■ pathology ■ diagnosis