CLINICAL PRACTICE

Initial Treatment of Hypertension

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 50-year-old black American has a blood pressure of 160/110 mm Hg on repeated measurements. He is 9 kg (20 lb) overweight, has a family history of hypertension, and smokes one pack of cigarettes daily. How should this patient be evaluated and treated?

THE CLINICAL PROBLEM

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Hypertension (systolic pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg) is present in one in four adults in the United States.[1] The prevalence is higher among blacks and older persons, especially older women. Table 1 shows the classification of blood pressure according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[2] Hypertension is a risk factor for stroke, myocardial infarction, renal failure, congestive heart failure, progressive atherosclerosis, and dementia.[3] Systolic pressure is a stronger predictor of cardiovascular events than is diastolic pressure,[4] and isolated systolic hypertension, which is common among older persons, is particularly hazardous.[5] There is a continuous, graded relation between blood pressure and the risk of cardiovascular disease; the level and duration of hypertension and the presence or absence of coexisting cardiovascular risk factors determine the outcome.[6] Treatment of hypertension reduces the risk of stroke, coronary artery disease, and congestive heart failure, as well as overall cardiovascular morbidity and mortality from cardiovascular causes. However, only 54 percent of patients with hypertension receive treatment and only 28 percent have adequately controlled blood pressure.[1]

STRATEGIES AND EVIDENCE

EVALUATION

Accurate measurement of blood pressure[7] and verification of elevated pressure on multiple occasions over time are important. Ambulatory or home blood-pressure monitoring[8] can identify "white-coat hypertension" (blood pressure that is elevated when measured during an office visit but that is otherwise normal) and prevent unnecessary treatment. White-coat hypertension, present in 20 percent of patients with elevated blood pressure, is associated with a lower cardiovascular risk than is sustained hypertension, but it may be a precursor of sustained hypertension and therefore warrants monitoring.

In addition to the history taking and physical examination, several tests are routinely indicated in patients with hypertension: urinalysis, complete blood count, blood chemical tests (measurements of potassium, sodium, creatinine, fasting glucose, total cholesterol, and high-density lipoprotein), and 12-lead electrocardiography. The evaluation should identify signs of cardiovascular, cerebrovascular, or peripheral vascular disease and other cardiovascular risk factors that are frequently present in patients with hypertension. Severe or resistant hypertension or clinical or laboratory findings suggesting

Table 1. Classification of Blood Pressure in Adults.*

Category	Blood Pressure
	mm Hg
Optimal	<120/<80
Normal	<130/<85
High normal	130–139 Systolic or 85–89 diastolic
Hypertension†	
Stage 1	140–159 Systolic or 90–99 diastolic
Stage 2	160–179 Systolic or 100–109 diastolic
Stage 3	≥180 Systolic or ≥110 diastolic

* The classification is for persons 18 years of age or older who are not taking antihypertensive drugs and are not acutely ill. When systolic and diastolic pressures fall into different categories, the higher category should be used to classify blood pressure. Isolated systolic hypertension is defined as a systolic pressure of 140 mm Hg or greater and a diastolic pressure below 90 mm Hg. Data are from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[2]

† The stage is determined on the basis of the average of two or more readings at each of two or more visits after an initial screening.

the presence of renal disease, adrenal hypertension (due to abnormal mineralocorticoid secretion or pheochromocytoma), or renovascular hypertension should be further investigated. Essential, or primary, hypertension, the focus of this article, is the diagnosis in over 90 percent of cases.

TREATMENT

The primary goal of the treatment of hypertension is to prevent cardiovascular disease and death. Coexisting cardiovascular risk factors increase the risks associated with hypertension and warrant more aggressive treatment. The five-year risk of a major cardiovascular event in a 50-year-old man with a blood pressure of 160/110 mm Hg is 2.5 to 5.0 percent; the risk doubles if the man has a high cholesterol level and triples if he is also a smoker.[9]

The benefits of lowering blood pressure, first demonstrated after short-term treatment of malignant hypertension,[10] have subsequently been demonstrated in all stages of hypertension. Trials involving patients with stage 1 or 2 hypertension showed that lowering systolic pressure by 10 to 12 mm Hg and diastolic pressure by 5 to 6 mm Hg reduces the risk of stroke by 40 percent, the risk of coronary disease by 16 percent, and the risk of death from any cardiovascular cause by 20 percent.[11,12] The higher the blood pressure and the number of risk factors, the greater the reduction in absolute risk (and the smaller the number needed to treat).

Determination of the need for drug therapy is based on a combined assessment of the blood-pressure level and the absolute risk of cardiovascular disease (Fig. 1). Patients with stage 1 hypertension can be treated with lifestyle modifications alone for up to one year, if they have no other risk factors, or for up to six months, if they have other risk factors. Drug treatment should be provided if blood pressure remains elevated after a trial of lifestyle modifications alone. Lifestyle modifications and antihypertensive therapy are indicated for patients with cardiovascular or other target-organ disease (renal, cardiac, cerebrovascular, or retinal disease) and for those with stage 2 or 3 hypertension. Patients with diabetes are at high risk, and drug therapy is indicated in such patients even if blood pressure is at the high end of the normal range.

Lifestyle Modifications

Table 2 lists lifestyle modifications recommended for all patients with hypertension. The Dietary Approaches to Stop Hypertension (DASH) study showed that eight weeks of a diet of fruits, vegetables, low-fat dairy products, whole grains, poultry, fish, and nuts, with limited fats, red meat, and sweets, reduced systolic pressure by 11.4 mm Hg and diastolic pressure by 5.5 mm Hg.[13] With sodium intake at a level below 100 mmol per day, systolic pressure was 3 mm Hg lower and diastolic pressure was 1.6 mm Hg lower than with the DASH diet and a higher level of sodium intake.[14]

Restriction of sodium intake to 2 g per day lowers systolic pressure, on average, by 3.7 to 4.8 mm Hg and lowers diastolic pressure, on average, by 0.9 to 2.5 mm Hg,[15,16] although the reductions vary from person to person beyond these ranges. Salt sensitivity is common in elderly patients with hypertension. Despite concern that salt restriction for all patients with hypertension might have adverse consequences,[17] moderate sodium restriction appears to be generally safe and effective[18] and is particularly effective in elderly persons.[19]

Whether lifestyle modifications can be sustained is a concern. Four years after enrollment in the Treatment of Mild Hypertension Study, patients with stage 1 hypertension had gained back half the weight lost after one year of intervention and were less successful at maintaining a low sodium intake and an increased level of physical activity than they had been at one year.[20] Nevertheless, lifestyle mod-

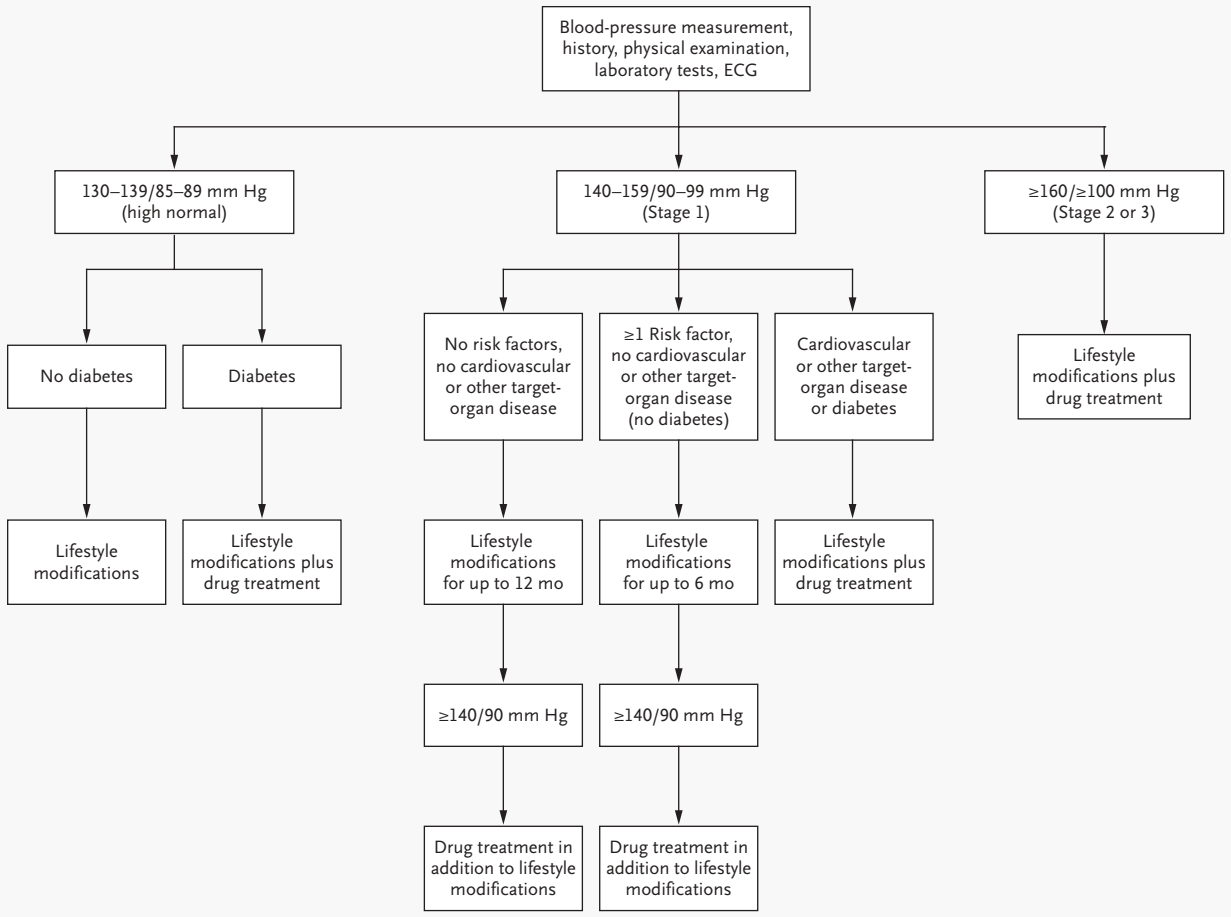

Figure 1. Treatment of Hypertension According to the Level of Blood Pressure and Cardiovascular Risk.

Two or more blood-pressure readings separated by two minutes should be averaged. If the pressure is at the high end of the normal range, it should be rechecked yearly. Stage 1 hypertension should be confirmed within two months. Patients with stage 2 hypertension should be evaluated and referred for care within one month; those with stage 3 hypertension should be evaluated immediately or within one week. If systolic and diastolic values are in different categories, the recommendations for the higher reading should be followed.

Laboratory tests include a complete blood count; measurements of potassium, sodium, creatinine, fasting glucose, total cholesterol, and high-density lipoprotein cholesterol; and urinalysis. ECG denotes electrocardiography. Cardiovascular or other target-organ disease denotes left ventricular hypertrophy, angina or prior myocardial infarction, prior coronary revascularization, heart failure, stroke or transient ischemic attack, nephropathy, peripheral arterial disease, and retinopathy.

For patients with multiple risk factors, clinicians should consider drugs as initial therapy along with lifestyle modifications. Clinically important risk factors include smoking, dyslipidemia, diabetes mellitus, an age of more than 60 years, male sex, postmenopausal status in women, and a family history of cardiovascular disease for women under the age of 65 years and men under the age of 55 years. Adapted from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[2]

ifications alone controlled blood pressure at four years in 59 percent of the patients.

Most clinical trials of lifestyle modifications have been underpowered or of insufficient duration to evaluate the effect of these interventions on major cardiovascular outcomes. However, lifestyle modifications should be encouraged, since they are safe and inexpensive and, when combined with drug therapy, may result in better blood pressure control and an improved quality of life.[21]

Treatment Goal for Blood Pressure

The risk of cardiovascular disease remains higher in treated patients with hypertension than in per-

sons with normal blood pressure, suggesting that treatment targets have not been low enough. Greater reductions in blood pressure have been shown to be safe and beneficial.[22,23] In the Hypertension Optimal Treatment trial, the risk of major cardiovascular events was lowest among patients whose blood pressure had been reduced to 138.5/82.6 mm Hg. An additional reduction did not further reduce the risk of events in nondiabetic patients, but it was not harmful. Among diabetic patients, the lowest rates of major cardiovascular events and death from cardiovascular causes were achieved with the lowest blood pressure. In patients over the age of 65 years, morbidity and mortality from cardiovascular disease are reduced when systolic pressure is lowered to a level below 160 mm Hg.[24] Whether levels below 140 mm Hg provide additional protection is unclear.

Table 2. Lifestyle Modifications to Prevent or Manage Hypertension.*

Modification	Comments
Maintain ideal body weight	Blood pressure reduced by 1.6/1.1 mm Hg for each 1 kg of weight loss
Engage in aerobic physical activity (30 to 45 minutes each day, most days of the week)	May reduce blood pressure as much as 13/8 mm Hg
Eat abundant fruits and vegetables and low-fat dairy products; reduce intake of saturated and total fats	May lower blood pressure by as much as 11.4/5.5 mm Hg after 8 weeks
Limit sodium intake to a maximum of 100 mmol per day (2.4 g of sodium or 6 g of sodium chloride)	May lower blood pressure by 3.7–4.8/0.9–2.5 mm Hg
Maintain adequate intake of dietary potassium (approximately 90 mmol per day)	
Maintain adequate intake of dietary calcium and magnesium	
Limit alcohol intake to a maximum of 30 ml (1 oz) per day (15 ml [0.5 oz] per day for women and people with low body weight)	
Stop smoking	

* Data are from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[2]

Choice of Antihypertensive Drugs

Most antihypertensive drugs reduce blood pressure by 10 to 15 percent. Monotherapy is effective in about 50 percent of unselected patients, and those with stage 2 or 3 hypertension often need more than one drug.[25] There have been few comparative trials of antihypertensive agents that have had sufficient power to demonstrate an advantage of one drug over another, and there is individual variation in responsiveness to drugs. Thus, the choice of therapy is based on a combined assessment of several characteristics of the patient: coexisting conditions, age, race or ethnic group, and the response to previously used drugs, including the presence or absence of adverse reactions.

A critical issue is whether a drug reduces cardiovascular morbidity and mortality. As compared with placebo, diuretics and beta-blockers reduce the risk of stroke, coronary heart disease, and overall mortality from cardiovascular disease in unselected patients with hypertension who do not have preexisting coronary disease, diabetes, or proteinuria.[11,12] A meta-analysis of trials involving more than 26,000 patients showed that, as compared with placebo, angiotensin-converting–enzyme (ACE) inhibitors reduce the risk of stroke, coronary heart disease, major cardiovascular events, death from cardiovascular causes, and death from any cause,[26] although the results were heavily dependent on a trial in which all the participants had preexisting cardiovascular disease or diabetes and some did not have hypertension.[27] Calcium-channel antagonists, as compared with placebo, reduce the risk of stroke, major cardiovascular events, and death from cardiovascular causes; however, these drugs do not significantly reduce the risk of coronary heart disease, heart failure, or death from any cause.[26]

The question of whether antihypertensive agents differ in their ability to prevent adverse outcomes has been difficult to answer.[28] Some data suggest potentially important differences. For example, ACE inhibitors were more effective than calcium-channel antagonists in preventing coronary heart disease in one trial,[29] but not in another, larger study.[30] A meta-analysis of clinical trials suggests that ACE inhibitors are more effective than calcium-channel antagonists in reducing the risk of heart failure but not in reducing the risk of stroke, death from cardiovascular disease, or death from any cause.[26] Losartan, an angiotensin-receptor antagonist, has recently been shown to be more effective than atenolol in reducing the risk of stroke.[31] Another meta-analysis suggests that calcium-channel antagonists may prevent stroke to a greater extent than diuretics or beta-blockers but have not been shown to provide similar protection against coronary heart disease.[32] The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, the largest randomized trial comparing

several antihypertensive agents as initial therapy, demonstrated that in patients older than 55 years (35 percent of whom were black and 19 percent of whom were Hispanic), diuretic-based therapy was as effective as treatment with calcium-channel antagonists or ACE inhibitors in preventing major coronary events.[33] Diuretic-based therapy was slightly more effective than treatment with calcium-channel antagonists in preventing heart failure and was more effective than treatment with ACE inhibitors in preventing stroke and heart failure. A smaller study of elderly white men and women with hypertension, reported in this issue of the *Journal*, showed that ACE-inhibitor–based therapy was slightly more effective than diuretic-based therapy in preventing myocardial infarction (only in men) but not stroke.[34]

On the basis of the available data, diuretics or beta-blockers remain appropriate for the initial treatment of uncomplicated hypertension, despite the concern that these agents may be associated with adverse metabolic effects (e.g., hyperuricemia and impaired glucose tolerance). Alternative drugs are preferable for patients with certain coexisting medical conditions (Table 3). In particular, ACE inhibitors and angiotensin-receptor antagonists are appropriate initial therapy in patients with diabetes mellitus, renal disease, or congestive heart failure[35,36] (though beta-blockers and diuretics are also useful in patients with heart failure); ACE inhibitors can also be used in patients with prior myocardial infarction or coronary artery disease. Short-acting calcium-channel antagonists cause a rapid, acute drop in blood pressure, which may precipitate coronary ischemia, and long-acting calcium-channel antagonists are therefore preferred when this class of agent is chosen.[37] Alpha-blockers relieve symptoms associated with prostatic hypertrophy. Since they are not as effective as other agents in reducing the risk of cardiovascular disease, they should be used as second- or third-line therapy.[33]

Other Considerations in the Choice of Therapy

Age and race have been shown to be determinants of the response to specific antihypertensive medications. The Department of Veterans Affairs Cooperative Study reported that younger whites had a

Table 3. Indications for the Use of Antihypertensive Drugs, Contraindications, and Side Effects.*

Class of Drug	Indications	Contraindications	Side Effects
Diuretics	Heart failure, advanced age, systolic hypertension	Gout	Hypokalemia, hyperuricemia, glucose intolerance, hypercalcemia (thiazides), hyperlipidemia, hyponatremia, impotence (thiazides)
Beta-blockers	Angina, heart failure, previous myocardial infarction, tachyarrhythmias, migraine	Asthma, chronic obstructive pulmonary disease, heart block	Bronchospasm, bradycardia, heart failure, impaired peripheral circulation, insomnia, fatigue, decreased exercise tolerance, hypertriglyceridemia
ACE inhibitors	Heart failure, left ventricular dysfunction, previous myocardial infarction, diabetic or other nephropathy or proteinuria	Pregnancy, bilateral renal-artery stenosis, hyperkalemia	Cough, angioedema, hyperkalemia, rash, loss of taste, leukopenia
Calcium-channel antagonists	Advanced age, systolic hypertension, cyclosporine-induced hypertension	Heart block (verapamil, diltiazem)	Headache, flushing, gingival hyperplasia, edema; short-acting calcium-channel antagonists may precipitate coronary ischemia
Alpha-blockers	Prostatic hypertrophy	Orthostatic hypotension	Headache, drowsiness, fatigue, weakness, postural hypotension
Angiotensin-receptor antagonists	ACE-inhibitor–associated cough, diabetic or other nephropathy or proteinuria, congestive heart failure	Pregnancy, bilateral renal-artery stenosis, hyperkalemia	Angioedema (rare), hyperkalemia

* Modified from the United Kingdom Prospective Diabetes Study Group.[23] ACE denotes angiotensin-converting enzyme.

good response to ACE inhibitors and beta-blockers, whereas older blacks had a better response to diuretics or calcium-channel antagonists.[25]

Hypertension is more severe and target-organ damage, particularly end-stage renal disease, more prevalent among blacks. Salt sensitivity is common, and sodium restriction should be encouraged. Although the magnitude of the blood-pressure response to monotherapy with a diuretic or a calcium-channel antagonist may be greater than the response to monotherapy with another agent, significant reductions occur with ACE inhibitors, angiotensin-receptor antagonists, and beta-blockers when an adequate dose is given.[38]

Side effects differ according to the class of antihypertensive drug (Table 3). Although adverse effects are reported by 10 to 20 percent of patients taking such drugs, the quality of life improves when hypertension is treated.[21] The Treatment of Mild Hypertension Study and the Department of Veterans Affairs Cooperative Study both demonstrated that among the five main classes of antihypertensive drugs (diuretics, beta-blockers, calcium-channel antagonists, ACE inhibitors, and alpha-blockers), no one drug is more acceptable than the others, except that sexual dysfunction is more common among men treated with the diuretic chlorthalidone.[21,25] Use of lower-cost, generic drugs that require less frequent doses can improve compliance.

Combination Therapy

The use of lower doses of two or more drugs with complementary mechanisms may lower blood pressure with fewer adverse effects than the use of higher doses of a single agent.[39] Most combination therapies include small doses of a diuretic, which potentiate the effects of other drugs (ACE inhibitors, angiotensin-receptor antagonists, or beta-blockers). Combination therapy may improve compliance and achieve the target blood pressure more rapidly.[40]

GUIDELINES

National and international groups have issued guidelines for the treatment of hypertension. The main differences among these guidelines are the criteria for initiating drug therapy in low-risk patients with stage 1 hypertension. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[2] and the World Health Organization–International Society of Hypertension[41] recommend stratification of patients into risk categories on the basis of age, sex, smoking status, presence or absence of diabetes, cholesterol level, presence or absence of preexisting cardiovascular disease, and presence or absence of target-organ damage (Fig. 1). Drug treatment is recommended for stage 1 or higher hypertension if blood pressure does not decrease after a certain period of lifestyle-modification counseling (6 to 12 months, according to the Joint National Committee guidelines). The British Hypertension Society and New Zealand guidelines recommend the use of tables that quantify a person's 5- or 10-year risk of a cardiovascular event; drugs are recommended only if the 5-year risk is at least 10 percent.[42,43] When drugs are indicated, the guidelines recommend those that have been shown to improve cardiovascular outcomes, with coexisting conditions and demographic characteristics taken into account.

AREAS OF UNCERTAINTY

Although moderate sodium restriction lowers blood pressure, the small effects, variability in response, and lack of a proven cardiovascular benefit have led to uncertainty about whether it should be broadly recommended. There is also uncertainty about whether specific properties of certain drugs result in differential effects on morbidity and mortality that are independent of the reduction in blood pressure.

The use of drugs in patients with a low absolute risk of cardiovascular disease is controversial. The rationale for withholding drugs from such patients is that some trials have shown that mortality among low-risk patients treated with drugs is similar to that in control groups.[44] However, given that even high-normal blood pressures (130 to 139/85 to 89 mm Hg) are associated with an increased risk of cardiovascular disease,[45] there is concern about withholding drugs from "low-risk" patients. Also, the feasibility of basing treatment decisions on the use of tables for calculating the absolute risk of cardiovascular disease has not been assessed.

The appropriate strategy for choosing the initial antihypertensive therapy is still unresolved. Some have proposed that the choice of treatment should be based on renin levels,[46] but this approach is not widely used. Whether combination therapy as the initial treatment leads to better control of blood pressure and a lower risk of cardiovascular disease than monotherapy is also unresolved. Finally, optimal blood-pressure targets remain to be determined, particularly for elderly patients.

CONCLUSIONS AND RECOMMENDATIONS

Hypertension affects 25 percent of adults in the United States and is adequately treated in less than 30 percent of them. Appropriate therapy can reduce blood pressure and cardiovascular morbidity and mortality.

Persons who have stage 1 hypertension and are at low risk for cardiovascular disease can be treated with lifestyle modifications for up to one year. Patients who have stage 1 hypertension and other cardiovascular risk factors or a higher stage of hypertension should be treated with drugs to reduce blood pressure to a level below 140/90 mm Hg, or to reduce pressure to 130/80 mm Hg or less if the patient has diabetes, renal disease, or both.

Diuretics and beta-blockers are appropriate as first-line therapy for patients without coexisting conditions. ACE inhibitors or angiotensin-receptor antagonists are recommended for patients with type 2 diabetes, kidney disease, or both and are also useful in patients with heart failure. Beta-blockers and ACE inhibitors are recommended in patients with prior myocardial infarction, and calcium-channel antagonists benefit elderly patients at risk for stroke. If blood pressure is not controlled with an optimal dose of a single drug, a second agent with a complementary mechanism of action should be added. Combination therapy provides more rapid control of blood pressure than does monotherapy and is therefore an initial treatment option for patients with stage 2 or 3 hypertension.

The patient in the case vignette should be advised to lose weight, stop smoking, engage in regular exercise, and modify his diet and should be screened for vascular disease and other cardiovascular risk factors. If no coexisting disease was detected, I would prescribe hydrochlorothiazide at a dose of 12.5 mg daily. If this dose did not control his blood pressure, I would increase it or add a second drug with complementary action — for example, an ACE inhibitor; the latter option would prevent the adverse metabolic effects of higher doses of diuretics.

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