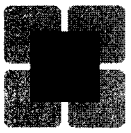

Mild hypertension: critical analysis of different therapeutic approaches

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■ In 1988 the fourth Joint National Committee (JNC IV) issued new guidelines for the detection, evaluation, and treatment of hypertension. Pharmacologic along with nonpharmacologic therapy is indicated for hypertensive patients whose diastolic blood pressures average ≥95 mmHg over a period of time and for patients who have a diastolic blood pressure of 90 mmHg to 94 mmHg with evidence of target organ disease and/or other major risk factors. In the absence of target organ disease and/or other major risk factors, a trial of nonpharmacologic treatment is recommended for patients with a diastolic blood pressure of 90 mmHg to 94 mmHg. The JNC IV report recommends initiating pharmacologic treatment with any one of the following classes of drugs: diuretics, beta blockers, calcium channel blockers, or ACE inhibitors. In general, diuretics and calcium channel blockers are especially indicated for elderly and black patients and beta blockers and ACE inhibitors for young and white patients, but there are many exceptions. In selecting the appropriate step-one agent for a given patient, the therapeutic "two-for-one" concept is emphasized whereby one antihypertensive drug may also be beneficial for a coexisting condition. Examples are: diuretics or ACE inhibitors in congestive heart failure; calcium channel blocking drugs or beta blockers in angina pectoris or paroxysmal supraventricular tachycardia; and beta blockers for migraine headache or senile tremor.

□ INDEX TERM: HYPERTENSION □ CLEVE CLIN J MED 1989; 56:337–345

MILD HYPERTENSION is defined as diastolic blood pressure of 90–104 mmHg (fifth phase) determined by averaging three readings on each of three separate visits. If the diastolic blood pressure is 90–95 mmHg, more than nine measurements should be made and the period of observation should be extended beyond the traditional three visits. In some cases, it is useful to have the patient or a family member measure the patient's blood pressure at home for two to three months to obtain 50 or 60 measurements before a decision is made about the need for drug therapy. In selected cases, 24-hour ambulatory blood pressure monitoring may be helpful in making this decision, although the expense of such monitoring is a deterrent to its widespread use.

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WHEN TO TREAT MILD HYPERTENSION

In addition to the diastolic blood pressure, factors to be considered in deciding whether to treat mild hypertension with pharmacologic agents include the presence

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TABLE 1
INDICATIONS FOR DRUG TREATMENT OF HYPERTENSION

Diastolic blood pressure (mmHg)	Target-organ damage		Other major risk factors	
	Present	Absent	Present	Absent
85–89	no	no	no	no
90–94	yes	?*	yes	?*
≤95	yes	yes	yes	yes

*Three- to six-month trial of nonpharmacologic therapy indicated first.

or absence of target organ damage and other major risk factors for atherosclerosis, such as cigarette smoking, hypercholesterolemia, diabetes mellitus, and a sedentary lifestyle (*Table 1*). Target organ damage includes history of transient ischemic attacks, angina pectoris, myocardial infarction, congestive heart failure, and stroke or renal disease, including proteinuria. Laboratory evidence of target organ damage includes left ventricular hypertrophy on the electrocardiogram or echocardiogram, cardiomegaly, nonspecific ST-T changes on the electrocardiogram, electrocardiographic evidence of remote myocardial infarction, serum creatinine greater than 1.5 mg/dL, and proteinuria 1+ or more.

During the deliberations of the fourth Joint National Committee (JNC IV) on Detection, Evaluation, and Treatment of High Blood Pressure,[1] the Committee agreed that diastolic blood pressure of <90 mmHg should not be treated pharmacologically and that diastolic blood pressure of ≥95 mmHg should be treated with both drugs and nonpharmacologic means.

Patients whose diastolic blood pressure is 90–94 mmHg and who have evidence of target organ damage or other major risk factors should be treated with both pharmacologic and nonpharmacologic methods from the outset. However, if the patient has no complications or risk factors, the patient should be given a three- to six-month trial of nonpharmacologic treatment, including dietary sodium restriction, weight reduction if appropriate, and reduction of alcohol consumption to a level of no more than one ounce of ethanol daily.

If the diastolic blood pressure is not <140/90 mmHg at the end of the trial, consideration should be given to prescribing a drug, although some members of the Committee would not prescribe drugs unless other risk factors or evidence of target organ disease are present. Nevertheless, patients with diastolic blood pressure of 90–94 mmHg who are not treated with drugs should be followed just as closely as those who are receiving drug treatment.

Although it was not discussed in the JNC IV report, systolic blood pressure should be considered in the decision about when to begin treatment for mild hypertension. Rutan et al[2] have shown that systolic blood pressure is a more important determinant of prognosis than diastolic blood pressure and that for any level of systolic blood pressure, diastolic blood pressure has little effect on prognosis. Consequently, it would seem prudent to treat a patient whose blood pressure was consistently at 160/90 mmHg, even in the absence of target organ disease and other risk factors. It would be more difficult to justify pharmacologic treatment for a patient whose average blood pressure is 120/90 mmHg.

It is perilous to wait for the appearance of target organ disease before antihypertensive therapy is initiated. In the Hypertension Detection and Follow-up Program (HDFP), patients who already had some evidence of target organ involvement at the beginning of the trial had more than three times the mortality rate in a five-year period compared to those who had no evidence of target organ disease. This was true even for those in the stepped-care (SC) group, which was treated aggressively to reach a goal blood pressure level.[3] However, compared to the referred-care (RC) group, the stepped care

TABLE 2
MILD HYPERTENSION: EFFECT OF TARGET ORGAN DAMAGE ON MORTALITY*

Target-organ damage	Stepped care		Referred care		% reduction in 5-year mortality
	No of Cases	Death rate†	No of cases	Death rate†	
Absent	3,402	4.5	3,462	5.8	22.4‡
Present	501	15.6	460	20.0	22.0§

*Mild hypertension defined as diastolic blood pressure of 90–104 mmHg.
†5-year mortality per 100
‡$P = .02$
§$P = .08$
From: Hypertension Detection and Follow-up Program Cooperative Group. Results of the Hypertension Detection and Follow-up Program. The effect of treatment on mortality in "mild" hypertension. N Engl J Med 1982; **307**: 976–980.

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group had a 22% lower five-year mortality rate even when target organ disease was present initially (*Table 2*). Treatment will be more effective if it is started before target organ disease becomes evident, but if the patient is not seen until target organ disease is present, it is still worthwhile to begin treatment in order to reduce mortality rates.

SELECTION OF DRUGS

The JNC IV report recommended that pharmacologic treatment be initiated with one of the following classes of drugs: diuretics, beta blockers, calcium channel blockers, or angiotensin-converting enzyme (ACE) inhibitors (*Figure 1*).[1] If the selected drug is ineffective or produces undesirable side effects, another Step 1 drug may be substituted. If the original drug is only partially effective, it may be desirable to add a second drug in step-wise fashion. If necessary, two or even three of the Step 1 drugs can be used in the same regimen since they have additive effects, with the possible exception of the combination of diuretics and calcium channel blockers.[4,5] However, other reports indicate that these two classes of drugs do have additive effects.[6,7]

Other options for Step 2 include the centrally acting adrenergic inhibiting drugs, alpha-1 blocking agents, or peripherally acting adrenergic inhibitors (*Table 3*). In general, however, the adrenergic inhibitors produce more side effects than other agents recommended for Step 1; for this reason, many physicians prefer to combine Step 1 agents if multi-drug treatment is required to control hypertension.

The direct vasodilator hydralazine (*Table 3*) is reserved for Step 3, which is seldom reached in managing mild hypertension. Unless an adrenergic inhibitor and diuretic are combined in the regimen, treatment with hydralazine frequently results in reflexive tachycardia and fluid retention. The direct vasodilator minoxidil is seldom if ever indicated in the treatment of mild hypertension because one of its side effects, hirsutism, is unacceptable, especially to women. It may also cause marked fluid retention that requires large doses of a diuretic to control.

Guidelines for selection of the appropriate Step 1 drug are outlined in *Table 4*. Gender seems to make no difference in responsiveness to antihypertensive agents. There are many exceptions to the general rule that elderly patients and black patients seem to respond better to diuretics or calcium channel blockers than to beta blockers and ACE inhibitors. In a review of three Veterans Administration trials, Freis et al[8] found that hypertensive patients older than 55 years seemed to have a greater decrease in blood pressure in response to diuretic therapy than younger patients; however, age did not seem to influence the response to a beta blocker or an ACE inhibitor.

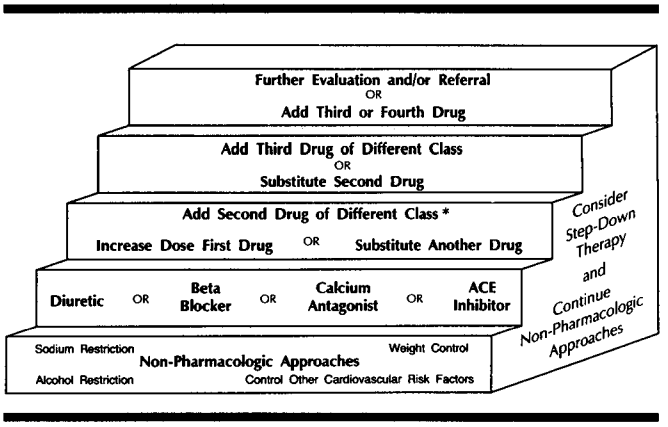

FIGURE 1. Individualized stepped-care therapy for hypertension. Reproduced by permission.[1]

In a multicenter double-blind trial in which hydrochlorothiazide was compared with enalapril as initial monotherapy in mild hypertension, black patients responded better to hydrochlorothiazide than to enalapril, whereas white patients tended to respond better to enalapril.[9] When the diuretic and ACE inhibitor were combined for patients who had not achieved normotensive blood pressure levels with either drug alone, black subjects responded as well as white subjects.

In a Veterans Administration trial that compared hydrochlorothiazide and propranolol, the two drugs were equally efficacious in white subjects, but the diuretic was more effective than propranolol in blacks.[10] Cubbedu et al[11] reported that verapamil was equally effective in blacks and whites when used as monotherapy in patients with mild hypertension, while propranolol was more effective in whites than in blacks, irrespective of age. Buhler et al[12] found that verapamil was more effective in elderly hypertensive patients than in young hypertensives, but this differential response to calcium channel blockers according to age has not been confirmed by others.[6,13–15] While Lijnen et al[16] reported an inverse correlation between age and change in both systolic and diastolic blood pressure in patients treated with captopril, Tuck et al[17] and Forette et al[18] have shown that ACE inhibitors are effective in elderly patients.

Whenever possible, it makes sense to prescribe antihypertensive drugs that might have a dual benefit (*Table 4*), such as a beta blocker or calcium channel blocker for

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TABLE 3
DOSES, SIDE EFFECTS, AND SPECIAL CONSIDERATIONS FOR ADRENERGIC INHIBITORS AND VASODILATORS

Type of drug	Dosage range (mg/d)*		Selected side effects§	Precautions and special considerations
	Initial	Maximum†		
Centrally acting alpha agonists				
Clonidine‡	0.1	1.2	Drowsiness, sedation, dry mouth, fatigue, sexual dysfunction. Localized skin reaction to clonidine TTS patch	Rebound hypertension may occur with abrupt discontinuance, particularly with prior administration of high doses or with continuation of concomitant beta-blocker therapy
Clonidine TTS (patch) ‖	0.1	0.3		
Guanabenz‡	4.0	64.0		
Guanfacine	1.0	3.0		
Methyldopa‡	250.0	2,000.0	Same as for above	May cause liver damage and Coombs-positive hemolytic anemia; use cautiously in elderly patients because of orthostatic hypotension; interferes with measurements of urinary catecholamine levels
Alpha-1 adrenergic blockers				
Prazosin‡	1.0–2	20.0	"First-dose" syncope, orthostatic hypotension, weakness, palpitations	Use cautiously in elderly patients because of orthostatic hypotension
Terazosin	1.0–2	20.0	Same as for prazosin	Same as for prazosin
Peripheral-acting adrenergic antagonists				
Guanadrel sulfate‡	10.0	100.0	Diarrhea, sexual dysfunction, orthostatic hypotension	Use cautiously because of orthostatic hypotension
Guanethidine	10.0	150.0	Same as for guanadrel	Same as for guanadrel
Rauwolfia alkaloids				
Whole root	50.0	100.0	Lethargy, nasal congestion, depression	Contraindicated in patients with history of mental depression; use with caution in patients with history of peptic ulcer
Reserpine	0.1	0.25		
Vasodilators			Headache, tachycardia, fluid retention	May precipitate angina pectoris in patients with coronary artery disease
Hydralazine‡	50.0	300.0	Positive anti-nuclear antibody test	Lupus syndrome may occur (rare at recommended doses)
Minoxidil‡	2.5	80.0	Hypertrichosis	May cause or aggravate pleural and pericardial effusions

* The dosage range may differ slightly from recommended dosage in *Physicians' Desk Reference* or package insert.
† The maximum suggested dosage may be exceeded in resistant cases.
‡ This drug is usually given in divided doses twice daily.
§ The listing of side effects is not all-inclusive, and health practitioners are urged to refer to the package insert for a more detailed listing.
‖ This drug is administered as a skin patch once weekly.
Adapted from the 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.[1]

hypertensive patients who also have angina pectoris, or a beta blocker (particularly propranolol) or a calcium channel blocker for hypertensive patients who also have migraine. Traditional beta blockers have a cardioprotective effect for patients who have had a myocardial infarction.[19,20] Verapamil, and to a lesser extent propranolol, reduce the frequency and severity of episodes of paroxysmal supraventricular tachycardia. ACE inhibitors are particularly effective in the management of congestive heart failure because they reduce preload (total peripheral resistance) and afterload (venodilatation). Beta blockers, especially propranolol, are effective in reducing senile tremor.

Cost should be considered in the selection of antihypertensive drugs because it can be a deterrent to compliance for patients with limited incomes.[21] Diuretics are by far the least expensive of Step 1 alternatives. However, in calculating expense, one must consider, in addition to the cost of the drugs themselves, the cost of laboratory tests to monitor for side effects as well as the cost of visits to the physician for supervision of treatment.

In the final analysis, the objective of treatment is to control blood pressure (systolic <140 mmHg and diastolic <90 mmHg) with minimal or no side effects and

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TABLE 4
SPECIAL INDICATIONS FOR ANTIHYPERTENSIVE DRUGS AS STEP I

Diuretics
Black patient
Elderly patient
Obesity
Congestive heart failure
Chronic renal failure
Beta-blockers
Young patient
White patient
Hyperkinetic circulation
Angina pectoris
Post myocardial infarction (cardioprotective effect)
Migraine headache
Senile tremor
Calcium chanel blockers
Elderly patient
Black patient
Angina pectoris
Paroxysmal supraventricular tachycardia
Migraine
ACE Inhibitors
Young patient
White patient
Congestive heart failure
Heavy proteinuria
Chronic renal disease
Diabetic glomerulosclerosis
Impotence from other drugs

with as few drugs in as small doses as possible.

STEP-DOWN

If hypertension has been well controlled for at least one year, it is frequently possible to reduce drug dosages gradually, one drug at a time, and perhaps even discontinue one drug in a multi-drug regimen. It is seldom possible to discontinue drugs entirely.

During the step-down process, the physician should monitor the patient's blood pressure carefully for a prolonged period since hypertension may not reappear for several months and sometimes not for a year or more after doses are reduced or drugs are eliminated from the regimen. Step-down is more likely to succeed in patients with mild hypertension than in those with moderate or severe hypertension, especially if nonpharmacologic measures are prescribed concomitantly.[22]

DIURETICS

Recommended doses and most common side effects of diuretics are listed in *Table 5*. It should be noted that the JNC IV report recommended lower starting doses of diuretics than previous reports. While the antihypertensive effects of diuretics are not dose-related above 25 or 50 mg daily of hydrochlorothiazide or chlorthalidone, metabolic side effects are dose-related.

The numerous advantages of diuretic therapy include ease of administration (one dose daily) and titration (no more than three steps, starting with 12.5 mg of hydrochlorothiazide or chlorthalidone), low cost, relative

TABLE 5
DOSES, SIDE EFFECTS, AND SPECIAL CONSIDERATIONS FOR DIURETICS

Type of drug	Dosage range (mg/d)* Initial	Maximum†
Thiazides and related sulfonamide diuretics		
Bendroflumethiazide	2.5	5.0
Benzthiazide	12.5–25	50.0
Chlorothiazide	125.0–250	500.0
Chlorthalidone	12.5–25	50.0
Cyclothiazide	1.0	2.0
Hydrochlorothiazide	12.5–25	50.0
Hydroflumethiazide	12.5–25	50.0
Indapamide	2.5	5.0
Methylclothiazide	2.5	5.0
Metolazone	1.25	10.0
Polythiazide	2.0	4.0
Quinethazone	25.0	100.0
Trichlormethiazide	1.0–2	4.0
Selected side effects:§ Hypokalemia, hyperuricemia, glucose intolerance, hypercholesterolemia, hypertriglyceridemia, sexual dysfunction, weakness, rash		
Precautions and special considerations: May be ineffective in renal failure; hypokalemia increases digitalis toxicity; may cause an increase in blood levels of lithium		
Loop diuretics‖		
Bumetanide‡	0.5	5.0
Ethacrynic acid‡	25.0	100.0
Furosemide‡	20.0–40	320.0
Selected side effects:§ Same as for thiazides		
Precautions and special considerations: Effective in chronic renal failure; hypokalemia and hyperuricemia as above		
Potassium-sparing agents		
Amiloride	5.0	10.0
Spironolactone	25.0	100.0
Triamterene	50.0	150.0
Selected side effects:§ Hyperkalemia		
Precautions and special considerations: Danger of hyperkalemia or renal failure in patients treated with an ACE inhibitor or a nonsteroidal antiinflammatory drug; may increase blood levels of lithium		

* The dosage range may differ slightly from recommended dosage in *Physicians' Desk Reference* or package insert.
† The maximum suggested dosage may be exceeded in resistant cases.
‡ This drug is usually given in divided doses twice daily.
§ The listing of side effects is not all-inclusive, and health practitioners are urged to refer to the package insert for a more detailed listing.
‖ Larger doses of loop diuretics may be required in patients with renal failure.
Adapted from the 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.[1]

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TABLE 6
DOSES, SIDE EFFECTS, AND SPECIAL PRECAUTIONS FOR BETA BLOCKERS

Drug†	Dosage range (mg/d)*	
	Initial	Maximum
Acebutolol	200.0	1,200.0
Atenolol	25.0	150.0
Carteolol	2.5	10.0
Labetalol‡§	200.0	1,800.0
Metoprolol	50.0	200.0
Nadolol	40.0	320.0
Penbutolol sulfate	20.0	80.0
Pindolol‡	10.0	60.0
Propranolol HCL‡	40.0	320.0
Propranolol, long-acting (LA)	60.0	320.0
Timolol maleate‡	20.0	80.0

Selected side effects:‖ Bronchospasm, peripheral arterial insufficiency, fatigue, insomnia, sexual dysfunction, exacerbation of congestive heart failure, masking of symptoms of hypoglycemia, hypertriglyceridemia, decreased HDL cholesterol (except for pindolol, acebutolol, and labetalol)

Precautions and special considerations: Should not be used by patients with asthma, chronic obstructive pulmonary disease (COPD), congestive heart failure, heart block (greater than first degree), and sick sinus syndrome; use with caution in insulin-treated diabetics and patients with peripheral vascular disease; should not be discontinued abruptly in patients with ischemic heart disease

* The dosage range may differ slightly from recommended dosage in *Physicians' Desk Reference* or package insert.
† The maximum suggested dosage may be exceeded in resistant cases.
‡ This drug is usually given in divided doses twice daily.
§ Combined alpha and beta blocker.
‖ The listing of side effects is not all-inclusive, and health practitioners are urged to refer to the package insert for a more detailed listing. Atenolol, metroprolol and acebutolol are cardioselective; pindolol, carteolol, penbutolol, and acebutolol have partial agonist activity (ISA).
Adapted from the 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.[1]

freedom from symptomatic side effects, and proven effectiveness, not only in reducing blood pressure but also in decreasing cardiovascular morbidity and mortality in clinical trials. Diuretics are particularly indicated for hypertension associated with obesity, chronic renal failure, or congestive heart failure because these conditions are characterized by fluid retention, which presumably aggravates the hypertension. A loop diuretic should be prescribed for patients with chronic renal failure, especially when the serum creatinine level is ≥2 mg/dL because thiazide diuretic agents lose their potency as serum creatinine levels rise.

The disadvantages of diuretics include sexual dysfunction in men, which occurs more commonly with diuretics than with some of the other drugs proposed for Step 1. The metabolic side effects of diuretics (hypokalemia, hypomagnesemia, hyperuricemia, hyperglycemia, hyperlipidemia) are also disadvantages, but if properly managed, they do not constitute contraindications to the use of diuretics except under unusual circumstances.

Hypokalemia can be prevented or corrected by prescribing a potassium-sparing diuretic in conjunction with the thiazide diuretic, although these agents are not necessary routinely and may lead to hyperkalemia if patients have renal insufficiency or if an ACE inhibitor is used in the same regimen. Diuretics may aggravate pre-existing diabetes in susceptible patients and may precipitate clinical diabetes in predisposed patients, although this risk is uncommon. Most diabetics tolerate a thiazide diuretic with little or no effect on the control of their diabetes.

Thiazide and related diuretics may cause an increase in serum cholesterol (mostly in the low density lipoprotein fraction) and triglycerides. Most long-term studies have failed to show any adverse effect on serum lipid concentrations beyond one year.[23–27] Furthermore, the effect seems to occur only in susceptible patients,[28] is apparent within the first four weeks of treatment,[28] and can be prevented or corrected by a low-fat diet.[29] An elevated concentration of serum cholesterol and/or triglycerides is not an *a priori* contraindication to the use of diuretics in the management of hypertension because the hyperlipidemic effect is more likely to occur in patients with normal serum levels of cholesterol and/or triglycerides than in patients with hyperlipidemia.[26,30]

If introduction of a diuretic causes serum levels of cholesterol and/or triglycerides to rise above normal, and the elevation cannot be eliminated by a low-fat, low-cholesterol diet, it would seem prudent to discontinue the diuretic rather than add an antilipidemic agent. On the other hand, when hypercholesterolemia is so severe that it can be managed only with drugs, there is no reason not to use a diuretic since it will not interfere with the effect of the lipid-lowering agent(s).

Diuretic-induced hyperuricemia so rarely leads to clinical gout that a hereditary predisposition probably explains the few cases in which it does occur. In the Hypertension Detection and Follow-up Program (HDFP), only 15 cases of gout were recorded in five years among 3,693 participants at risk.[31] Diuretic-induced hyperuricemia in the absence of gout is not an indication for antiuricemic therapy, nor is it a contraindication to continuation of the diuretic.

BETA BLOCKERS

All beta blockers (*Table* 6) have more or less equivalent antihypertensive potency, but the cardioselective agents are less likely than nonselective drugs to worsen

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intermittent claudication, to prolong hypoglycemia in insulin-dependent diabetics, and to aggravate bronchospasm in patients with chronic obstructive pulmonary disease. Since cardioselectivity is inversely related to dose, even the cardioselective agents may produce considerable beta-2 blockade with the higher doses sometimes needed for control of hypertension. The beta blockers without intrinsic sympathomimetic activity (ISA) reduce blood pressure largely by reducing cardiac output, whereas the ISA drugs reduce total peripheral resistance, to some extent at least. Although this latter mechanism may be a more physiologic way to reduce blood pressure, the reduction is no greater. ISA beta blockers reduce pulse rate less than the non-ISA beta blockers. The post-myocardial infarction cardioprotective effect of the traditional beta blockers does not seem to be shared by the ISA beta blockers or by the combined alpha and beta blocker labetalol.

For the younger hypertensive patient with hyperkinetic circulation manifested by resting tachycardia, cardiac awareness, and a relatively wide pulse pressure, a beta blocker is the agent of choice because this type of hypertension is usually due to high cardiac output with fairly normal total peripheral resistance. The beta blocker reduces cardiac output, slows the heart rate, and normalizes blood pressure.

Like diuretics, beta blockers have been shown to reduce cardiovascular morbidity and mortality in large, controlled clinical trials.

The disadvantages of beta blockers include a fairly high incidence of central nervous system side effects (sleep disturbances, fatigue, lethargy) and contraindications (more than first degree heart block, asthma, sick sinus syndrome, congestive heart failure). Beta blockers, like diuretics, may cause metabolic side effects, including impaired glucose tolerance, depressed high-density lipoprotein cholesterol, and increases in total serum cholesterol and triglycerides. Unlike diuretics, however, lipid abnormalities induced by beta blockers tend to persist as long as the drug is administered.

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

Theoretically, ACE inhibitors should be effective only for patients with angiotensin II-dependent hypertension, but in fact, they reduce blood pressure for a broad spectrum of hypertensive patients, irrespective of plasma renin activity. These vasodilating agents reduce blood pressure by decreasing peripheral vascular resistance without inciting reflex tachycardia.

One of the advantages of ACE inhibitors is their low incidence of side effects. In a quality of life assessment of 626 men by Croog et al,[32] captopril detracted from quality of life to a lesser extent than methyldopa or propranolol. A diuretic reserved as the second-step drug was added to achieve control of hypertension in 36% of patients taking captopril, 31% of those taking methyldopa, and 22% of those taking propranolol. Only 18.8% of patients complained of worsened sexual function while taking captopril, compared to 24.1% for methyldopa and 25.6% for propranolol. A disadvantage of treatment with ACE inhibitors is that they are expensive.

A dry, irritating cough is probably the most frequent symptomatic side effect of ACE inhibition, although it is not associated with bronchospasm.[33] Proteinuria and bone marrow depression are rare side effects when ACE inhibitors are administered in recommended doses (*Table 7*). Although ACE inhibitors do not adversely affect serum lipids or uric acid, they tend to increase serum potassium. Enalapril seems to have a slightly favorable effect on blood glucose and hemoglobin A_{1C} in hypertensive diabetics.[34] There is emerging evidence, mostly from animal studies, but also from short-term observations in humans, that ACE inhibition reduces proteinuria for patients with diabetic nephropathy.[35] It may retard glomerulosclerosis by selectively dilating the efferent (post-glomerular) arteriole, thus reducing intra-

TABLE 7
DOSES, SIDE EFFECTS, AND SPECIAL PRECAUTIONS FOR ACE INHIBITORS

Drug	Dosage range (mg/d)*	
	Initial	Maximum†
Captopril‡	25–50.0	300.0
Enalapril maleate	2.5–5	40.0
Lisinopril	5.0	40.0

Selected side effects:§ Rash, cough, angioneurotic edema, hyperkalemia, dysgeusia

Precautions and special considerations: Can cause reversible, acute renal failure in patients with bilateral renal arterial stenosis or unilateral stenosis in a solitary kidney; proteinuria may occur (rare at recommended doses); hyperkalemia can develop, particularly in patients with renal insufficiency; rarely can induce neutropenia; hypotension has been observed with initiation of ACE inhibitors, especially in patient with high plasma renin activity or in those receiving diuretic therapy

* The dosage range may differ slightly from recommended dosage in *Physicians' Desk Reference* or package insert.
† The maximum suggested dosage may be exceeded in resistant cases.
‡ This drug is usually given in divided doses twice daily.
§ The listing of side effects is not all-inclusive, and health practitioners are urged to refer to the package insert for a more detailed listing.
Adapted from the 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.[1]

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TABLE 8
DOSES, SIDE EFFECTS, AND SPECIAL PRECAUTIONS FOR CALCIUM ANTAGONISTS

Drug	Dosage range (mg/d)*		Selected side effects‡	Precautions and special considerations
	Initial	Maximum†		
Diltiazem§	60.0	360.0	constipation	may cause liver dysfunction
Diltiazem SR (long-acting)	60.0	360.0	–	–
Verapamil§	120.0	480.0	constipation	may cause liver dysfunction
Verapamil SR (long-acting)	120.0	480.0	constipation	may cause liver dysfunction
Nicardipine§	60.0	120.0	tachycardia	–
Nifedipine§	30.0	180.0	tachycardia	–
Nitrendipine	5.0	40.0	tachycardia	–

* The dosage range may differ slightly from recommended dosage in *Physicians' Desk Reference* or package insert.
† The maximum suggested dosage may be exceeded in resistant cases.
‡ The listing of side effects is not all-inclusive, and health practitioners are urged to refer to the package insert for a more detailed listing. All calcium antagonists can cause headache, flushing, and edema.
§ This drug is usually given in divided doses three or four times daily.
Adapted from the 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.[1]

capillary pressure in the glomerulus without compromising blood flow. Further observations in humans are needed to confirm the latter possibility.[36]

If ACE inhibitors are prescribed for patients with chronic renal disease, especially when azotemia is present, serum creatinine and potassium should be monitored frequently. Hyperkalemia, with or without an increase in serum creatinine, may occur as a result of ACE inhibition. Potassium-sparing diuretics and potassium supplements should not be given as part of the same regimen with an ACE inhibitor, especially in azotemic patients.

ACE inhibitors may cause acute renal failure in patients who have severe bilateral renal artery stenosis or severe stenosis in the artery to a solitary kidney, presumably because the glomerular filtration rate is dependent upon angiotensin II-mediated constriction of the efferent arteriole, which is abolished by ACE inhibition. For the same reason, ACE inhibition has been associated with acute renal failure when given to patients with severe heart failure who also have hypovolemia.[37]

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers (*Table 8*) are peripheral vasodilators that reduce blood pressure by decreasing total peripheral resistance. They have variable effects on the myocardium. Verapamil slows the heart rate, decreases atrioventricular conduction, and has a negative inotropic effect on myocardial contractility, similar to the effect of beta blockers. Consequently, verapamil should not be prescribed for patients with greater than first degree heart block or left ventricular failure. In general, beta blockers and verapamil should not be prescribed in the same regimen for patients with left ventricular dysfunction. Nifedipine and nitrendipine, however, have little if any effect on the myocardium; in fact, nifedipine may cause reflexive tachycardia for some patients. The effect of diltiazem on the myocardium is distinctly less than that of verapamil. Diltiazem has been shown to have a cardioprotective effect for 12 to 52 months after an acute myocardial infarction, provided pulmonary congestion was not present at the time of the acute infarct.[38] When pulmonary congestion was present, diltiazem had an adverse effect on survival compared to placebo.

Verapamil in the sustained-release form and nitrendipine may be given once daily. A relatively new sustained release preparation of diltiazem can be given twice daily. Nifedipine usually has to be administered three times daily because of its short duration of action. Symptomatic side effects are more troublesome with nifedipine than with verapamil, whereas those of diltiazem seem to fall in the intermediate range.

A calcium channel blocker is preferred to a beta blocker for hypertensive patients with angina pectoris who also have bronchospastic disease, Raynaud's disease, or intermittent claudication. While calcium channel blockers do not have metabolic side effects, they are as expensive as ACE inhibitors.

CONCLUSION

The individualized stepped-care approach to the management of hypertension as proposed by the fourth Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure is advantageous for both the physician and the patient. This approach

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gives the physician more flexibility in choice of drugs, and benefits the patient by enhancing effectiveness and minimizing side effects of antihypertensive regimens.

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