Adequate control of blood pressure poses challenges for hypertensive patients and their physicians. Success rates of greater than 80% in reducing blood pressure to target values among high-risk hypertensive patients reported by several recent clinical trials argue that effective medications currently are available. Yet, only 34% of hypertensive patients in the United States are at their goal blood pressure according to the most recent national survey. Rational selection of antihypertensive drugs that target both the patient’s blood pressure and comorbid conditions coupled with more frequent use of low-dose drug combinations that have additive efficacy and low adverse-effect profiles could improve significantly US blood pressure control rates and have a positive impact on hypertension-related cardiovascular and renal mortality and morbidity. This article reviews the pharmacokinetic and pharmacodynamic principles that underlie the actions of drugs in each of the classes of antihypertensive agents when used alone and in combination, provides practical pharmacologic information about the drugs most frequently prescribed for treatment of hypertension in the outpatient setting, and summarizes the current data influencing the selection of drugs that might be used most effectively in combination for the majority of hypertensive patients whose blood pressures are not controlled adequately by single-drug therapy.
and patients who already have experienced a stroke, myocardial infarction, renal damage, or congestive heart failure.

**General Principles of Antihypertensive Drug Therapy**

Many antihypertensive drugs exhibit a dose-response relationship similar to that shown in Figure 1A. One characteristic of this relationship is a threshold dose below which there is no discernible effect of the drug. When a change in systolic or diastolic blood pressure is the measured response, the Food and Drug Administration usually has required that the manufacturer define the lowest effective dose of the drug under consideration and this information is included in the drug's product monograph. Once the dose is higher than this threshold there usually is a relatively steep increase in the response when plotted against the logarithm of the dose until further dosage increases produce no additional response. The dose that produces a concentration of the drug which exerts 50% of the maximum effect is the EC\textsubscript{50}. The EC\textsubscript{50} is the dose that produces 50% of the maximum effect. The characteristics of the dose-response relationship for a particular drug are defined not only by the dose of the drug but by the response against which it is plotted. For example, the maximum antihypertensive effect of an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin-receptor blocker (ARB) may be achieved at a dose that does not maximize the effect of these drugs on proteinuria.\textsuperscript{3,5} In fact, a compelling argument...
can be made that the characteristics for the dose-response relationship of ARBs and proteinuria is not known because the maximum effective dose of any ARB on proteinuria has not been identified. This also may apply to actions of these agents on the heart, vasculature, and brain related to but not totally linked to blood pressure.

As shown in Figure 1B, the dose versus adverse-effect relationship for most antihypertensive drugs is different both quantitatively and qualitatively from that for the dose versus response relationship. For most drugs, adverse events become apparent and begin to increase in frequency at doses higher than those at which a response first is noted. One goal of therapy is to treat patients with doses of drugs that maximize the desired effect but minimize the frequency of adverse effects. An example of the application of this principle to practical therapeutics is the current dosing recommendations for thiazide diuretics compared with the recommendations from 20 years ago. The results of clinical pharmacology trials have documented progressive reductions in blood pressure with daily doses of hydrochlorothiazide from 3.125 to 25 mg that have few or no adverse metabolic or electrolyte consequences such as hypokalemia, hypomagnesemia, hyperuricemia, dyslipidemia, or hyperglycemia in the vast majority of patients. As the dose was increased to greater than 25 mg daily, however, there was little or no further decrease in blood pressure but an almost linear dose-dependent decrease in serum potassium level and an increased frequency of other unwanted metabolic effects. In clinical trials, patients who developed hypokalemia, even with low doses of diuretics, were at greater risk for cardiovascular events than patients who remained normokalemic, particularly if they had electrocardiographic abnormalities at entry into the trial.

If a drug at any given dose is less than optimally effective but has a low adverse-effect profile, one option is to increase the dose of the drug. This approach, however, is likely to increase the number of adverse effects (Fig 1C). An alternative approach is to add a second drug at a low dose. It is desirable to select 2 drugs whose combined efficacy is superior to either drug alone while maintaining a low frequency of adverse effects (Fig 1D). There are numerous examples of this approach, the most frequent being the addition of a low dose of a diuretic to an ACEI, ARB, or β-adrenergic-receptor antagonist (β-blocker). In fact, the actions of ACEIs and ARBs that ultimately reduce the production of aldosterone serve to lessen the incidence of hypokalemia and resultant metabolic consequences produced by diuretics. The addition of a second drug to alter the adverse effects of the first drug, even if the second drug adds little to the efficacy of the combination, also is common. Drug combinations that concurrently increase efficacy and reduce adverse effects include an ACEI and a diuretic, an ARB and a diuretic, an ACEI and a dihydropyridine calcium channel antagonist (DCA). As noted earlier, the incidence of hypokalemia is reduced when drugs that interdict the renin-angiotensin system are combined with potassium-loosing diuretics. When ACEIs are given together with a DCA, peripheral edema, the most common adverse effect of DCAs, is reduced. Sometimes drugs are combined because the actions of the second drug reduce unwanted side effects of the first drug, even though the second drug adds little to the overall efficacy of the combination. Preparations combining potassium-loosing and potassium-sparing diuretics have been available for many years. The potassium-sparing component adds little to the antihypertensive efficacy of the potassium-decreasing diuretic but blunts the hypokalemia and selected other adverse metabolic consequences.

Decisions about which drugs or drug combinations to select for individual patients should be based on known properties of the drugs both for decreasing blood pressure and for reducing or preventing cardiovascular and renal target organ damage, on medical information obtained by a thorough risk assessment, and on demographic and psychosocial characteristics of the patient.

**Single-Drug Treatment of Hypertension**

Although a majority of patients with hypertension will require more than 1 drug to control blood pressure to optimal levels, some patients whose pretreatment blood pressures are 20/10 mm Hg or less above their target value (140/90 mm Hg for uncomplicated stage 1 hypertension or 130/80 mm Hg for those with diabetes or chronic kidney disease according to guidelines published in the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7 guidelines)) may be candidates for single-drug therapy. All drugs approved by the US Food and Drug Administration for the treatment of hypertension have been shown to decrease blood pressure in most hypertensive patients compared with placebo. Clinicians can expect that most commonly used antihypertensive drugs will decrease systolic blood pressure, on average, 10 mm Hg and decrease diastolic blood pressure 5 mm Hg. As with any generalization, there are some notable exceptions to the 10/5 rule that influence the choice of drug class for the treatment of selected patient groups. African Americans as a group do not experience as great a reduction in blood pressure with renin-angiotensin system–inhibitory drugs, the ACEIs, and the ARBs, as they do with diuretics and DCAs. On average, a reduction of 6 to 8 mmHg systolic and 3 to 4 mmHg diastolic can be expected in this ethnic group with optimum doses of these drugs. In contrast, thiazide-type diuretics and DCAs were among the most effective antihypertensive agents for controlling diastolic blood pressure in younger and older African-American men after 1 year of single-drug therapy. Patients who achieve blood pressure control initially with a single drug should continue to be evaluated periodically because, as was observed in the ALLHAT trial, blood pressure control with monotherapy may be lost over time and additional drug therapy may be required to maintain control.
Diuretics not only decrease blood pressure by promoting the renal excretion of salt and water, thereby reducing extracellular fluid volume and cardiac output, but they also reduce intracellular sodium and calcium levels, leading to vasorelaxation and a reduction in peripheral vascular resistance with long-term use. Thiazide-type diuretics are effective antihypertensive agents in patients with normal or modestly impaired renal function as long as their dietary sodium intake does not exceed their renal sodium excretion. They become ineffective, however, in patients whose glomerular filtration rates are less than approximately 25 mL/min or their serum creatinine level is 2 mg/dL or greater. In these latter patients, intense sodium reabsorption in the proximal tubule and loop of Henle leaves little sodium available for sodium-potassium exchange in the distal tubule and a loop diuretic should be prescribed instead of a thiazide. Numerous clinical trials have shown that thiazide-type diuretics reduce fatal and nonfatal cardiovascular events in hypertensive patients.

Although these agents are being recommended by some as initial therapy for all uncomplicated hypertensive patients, they do have adverse effects that must be considered when deciding to prescribe one of the drugs in this class to a specific hypertensive patient. Of particular concern is the development of hypokalemia, which is linked closely to the presence of impaired glucose tolerance and to insulin resistance. The development of these adverse effects may play a part in the higher rate of discontinuation of drugs in this class than with drugs in the ARB or ACEI class. As noted earlier, adverse effects can be minimized by treating with lower rather than high doses of diuretics. For those individuals at risk for development of metabolic syndrome or overt diabetes because of obesity, a strong family history or 2 but not 3 components of the metabolic syndrome such as hypertension and dyslipidemia (coexistent in an estimated 27 million Americans) or hypertension and obesity, therapy with a diuretic should be initiated with some caution. The results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial suggested that adverse metabolic consequence in northern European patients treated with a diuretic to which a β-blocker could be added were substantially more common than those in patients treated with an ARB to which a DCA could be added for blood pressure control if needed.

In the ALLHAT trial the incidence of new-onset diabetes was 11.6% in the group randomized to chlorthalidone compared with 9.8% in the amlodipine group and 8.1% in the lisinopril group. This association of a higher rate of new-onset diabetes with thiazide-type diuretics compared with DCAs and ACEIs is of particular concern in light of the recent report by Verdecchia et al in which, after a median follow-up period of 6 years, the cardiovascular risk for patients who developed diabetes after starting antihypertensive therapy was 2.9 times higher than patients who did not develop diabetes and was only slightly less than patients who already had diabetes (3.6-fold higher) when therapy was started. For a more thorough review of the electrolyte and metabolic effects of diuretics the reader is referred to a recent excellent review of this topic by Sica.

The similarities and differences between chlorthalidone and hydrochlorothiazide have received considerable attention recently after the publication of the ALLHAT trial results in which chlorthalidone was found to be equivalent to either a DCA (amlodipine) or an ACEI (lisinopril) in its effects on the combined primary end point of coronary heart disease mortality and morbidity. Most physicians in this country do not prescribe chlorthalidone but instead prescribe hydrochlorothiazide (HCTZ). There are differences in the pharmacokinetic properties of the 2 drugs of which the prescribing clinician should be aware. Chlorthalidone is estimated to be 50% to 75% more potent than HCTZ and has a much longer half-life (45-60 hours after repeated dosing) than HCTZ (8-15 hours after repeated dosing). The duration of action of both drugs, however, is much longer than predicted by the half-life and once-daily dosing with either drug appears to provide effective blood pressure control over 24 hours.

β-Blockers

β-adrenergic–receptor antagonists or β-blockers have an important role in the therapy of a variety of cardiovascular conditions including ischemic heart disease, cardiac arrhythmias, congestive heart failure, and hypertension. The pharmacologic effects of β-receptor blockers are caused by multiple factors including the chemical characteristics of specific β-blockers (some are lipophilic and some are hydrophilic); the relative affinity of a particular drug for β1 versus β2 receptors and the tissue distribution of those receptors; the capacity of a drug to activate partially as well as to inhibit β-receptors (partial agonist action or intrinsic sympathomimetic activity); the inhibitory actions of a drug on receptors other than β-receptors such as combined α- and β-receptor antagonists like carvedilol and labetolol; and the drug’s pharmacokinetic characteristics such as bioavailability, renal versus hepatic metabolism, and the extent of first-pass metabolism by the liver. Lipophilic β-blockers such as timolol, propranolol, and metoprolol penetrate the blood-brain barrier more readily than do the hydrophilic β-blockers such as atenolol and esmolol; this characteristic might explain the higher frequency of central nervous system adverse effects in patients taking lipophilic β-blockers. Some β-blockers exhibit greater selectivity for β1 than β2 receptors and are referred to as cardioselective. This term, however, is relative because the blockade of both β1 and β2 receptors occurs at higher doses. Although the survival benefit of both cardioselective and nonselective β-blockers after myocardial infarction is well established, the results of 2 meta-analyses have suggested that β-blockers with intrinsic sympathomimetic activity do not provide the same cardiovascular outcomes benefit as do β-blockers without this property.

The mechanisms of blood pressure reduction by β-blockers is attributed primarily to decreased cardiac output resulting from a slowing of heart rate and, to a much lesser extent, a decrease in contractility. Peripheral resistance also is reduced by a β2-receptor–mediated reduction in renin release.
with consequent reduction in angiotensin II concentrations. A sympatholytic effect also occurs by blocking \( \beta_1 \)-receptor-mediated increases in norepinephrine release from sympathetic nerve terminals. These mechanisms of action have implications for the effectiveness of \( \beta \)-blockers in African Americans and in the elderly. Because African Americans tend to have low-renin and salt-sensitive hypertension, it is not surprising that \( \beta \)-blockers reduce blood pressure much less in this ethnic group than in Caucasian hypertensive patients. African Americans with heart failure, however, experience the same reduction in mortality and morbidity with \( \beta \)-blockers as do Caucasian patients. The elderly tend not only to have a higher incidence of low-renin hypertension than younger individuals but also to exhibit blunted \( \beta \)-receptor–mediated responses to \( \beta \)-agonists. These differences may explain why the elderly derive less survival benefit from \( \beta \)-blockers than do their younger counterparts.

A concern has been expressed in the literature about using \( \beta \)-blockers in patients with cardiovascular disease who have concomitant reactive airway disease. \( \beta \)-blockers, especially those with a high affinity for the \( \beta_1 \) receptor, are relatively contraindicated in patients with asthma and chronic lung disease with a significant bronchospastic component. The results of a recent meta-analysis of studies that have explored the use of cardioselective \( \beta \)-blockers in these patients suggest that cardioselective \( \beta \)-blockers not only are safe but actually may enhance sensitivity to inhaled \( \beta \)-agonists because of receptor activation.

Although \( \beta \)-blockers have been used extensively in hypertension and related disorders for a number of years, a recent extensive re-analysis of various trials suggested that atenolol exerts no therapeutic benefits whatsoever. The investigators surveyed the major trials in hypertension that used atenolol and concluded that it was no better than a placebo and significantly inferior to other antihypertensive drugs. Whether these findings are applicable to other \( \beta \)-blockers is unclear. Nevertheless, this provocative re-appraisal of atenolol casts doubt on the relative use of \( \beta \)-blocker therapy in patients with hypertension. Much debate can be expected as a result of this observation from atenolol-based studies. Some credence to these observations is gained by the demonstration of reduced benefits from atenolol therapy compared with losartan in the Losartan Intervention for Endpoint Reduction of reduced benefits from atenolol therapy compared with an atenolol-based regimen at equivalent blood pressure levels decreased the risk for fatal and nonfatal strokes in a high-risk population. Thus, one could argue for angiotensin-receptor blockade over \( \beta \)-blockade for superior target organ protection in patients with hypertension, at least in those older patients with left ventricular hypertrophy.

**Calcium-Channel Blockers**

The class of drugs called calcium-channel blockers (CCBs) can be separated into 3 groups on the basis of their chemical structures: the phenylalkylamines (verapamil-like), the benzothiazepines (diltiazem-like), and the dihydropyridines (nifedipine-like). All of the drugs in this class that currently are available commercially in the United States bind to and inhibit L-type but not P-, N-, or T-type calcium channels. Drugs in each of the 3 groups bind at different adjacent sites on the polypeptide chain that comprises the pore-forming \( \alpha_{1c} \) subunit of the L-type calcium channel, suggesting that they could have complementary effects when given together in a clinical setting. The actions of the CCBs are based on regional differences in the expression of L-type calcium channels, the affinity of a specific CCB for the channel in a particular tissue, and on the varied biochemical pathways that mediate the response to different agonists which modulate channel activity. The pharmacodynamics of verapamil and diltiazem are similar to each other and both are distinct from those of the dihydropyridines. Verapamil and diltiazem often are called nondihydropyridine calcium antagonists (NDCAs) to distinguish their actions from those of the DCAs. The NDCAs reduce the sino-atrial node firing rate and the atrioventricular conduction rate because they bind more avidly to the L-type calcium channels in those cardiac cells than do the DCAs at therapeutic concentrations. Accordingly, they are considered to be rate-control CCBs. These properties provide the rationale for their use in the treatment of atrial fibrillation, atrial flutter, and nodal re-entrant tachycardias without accessory conducting pathways. These drugs also reduce cardiac contractility whereas DCAs do not have this effect at doses used clinically. In general, the DCAs, especially nifedipine, are more potent arterial vasodilators than the NDCAs; they have far less effect on venous dilation, a property that accounts for the significant incidence of peripheral edema. Because of studies showing that the rapid, potent, and unpredictable hypotensive effect of native nifedipine increases the risk for angina and myocardial infarction in susceptible individuals, this drug is not recommended for the treatment of hypertensive urgencies or emergencies.

After oral administration, most of the CCBs undergo extensive first-pass metabolism that contributes to the relative short half-life of verapamil, diltiazem, and nifedipine, and requires they be taken 2 or 3 times daily to maintain 24-hour efficacy. The availability of extended-release formulations of these 3 drugs allows them to maintain more constant blood levels for 24 hours when given once daily. DCAs such as amlodipine and felodipine that are subject to less extensive hepatic metabolism have a substantially longer duration of action and the native drugs are effective when given only once daily. With the exception of nifedipine and diltiazem, the CCBs are formulated as racemic mixtures. It is the \( S \)-enantiomer of the CCB that binds to the L-type calcium channel. Recent studies indicate that the \( R \)-enantiomer of amlodipine is responsible for the activation of nitric oxide synthase by this dihydropyridine CCB, an effect not shared with diltiazem or nifedipine. This \( R \)-enantiomer also potentiates the nitric oxide synthase–stimulatory effect of the ACEI, ramiprilat. It is not known if stereoisomers of other CCBs have biological effects.

All of the CCBs are metabolized to less-active or inactive metabolites by the cytochrome P450 family of enzymes, predominantly by CYP3A. Concurrent administration of CCBs
with either inducers or inhibitors of the CYP3A enzyme can result in drug-drug interactions of which the clinician should be aware. Co-administration of digoxin with either verapamil or diltiazem results in a 40% to 90% increase in serum digoxin concentrations. Rifampin and phenytoin, both inducers of CYP3A4, decrease verapamil and diltiazem concentrations whereas cimetidine, a CYP3A4 inhibitor, has the opposite effect. The CCBs all increase cyclosporine blood levels in organ transplant patients taking this immunosuppressive drug. For a more thorough review of the clinical pharmacology of the CCBs with extensive references, the reader is referred to an excellent review of this drug class by Abernethy and Schwartz. 

ACEIs

Since captopril, the first orally active nonpeptide inhibitor of ACEs, was approved in 1986, it has become increasingly evident that blockade of the renin-angiotensin-aldosterone system not only decreases blood pressure in hypertensive patients but also reduces injury to the heart, kidney, brain, and blood vessels. The ACEIs have been shown in randomized, controlled, clinical trials to decrease mortality and morbidity in congestive heart failure after recent and remote myocardial infarction, blunt the decline in glomerular filtration rate, reduce incidence of stroke, produce greater regression of left ventricular hypertrophy than non–RAAS-blocking therapies, reduce albuminuria, delay the onset of new diabetes, and improve endothelial function (see Cushnern for review). This last effect is thought to occur because of an inhibition of angiotensin-dependent increase in oxidative stress and the resulting decrease in nitric oxide activity and concurrent increase in inflammatory cytokines and chemokines. 

Of the 10 ACEIs for oral administration currently marketed in the United States (benazepril, quinapril, ramipril, moexipril, perindopril, trandolapril, fosinopril, enalapril, lisinopril, and captopril), all except lisinopril and captopril are prodrugs that require hydrolysis by esterases in the liver or intestine to the active dicarboxylic acid form. Although the pharmacokinetic properties of the drugs in this class vary somewhat, these differences usually are not critical in the choice of a specific ACEI because all of the drugs in this class, with the exception of captopril, usually exhibit little or no dose-limiting toxicity. Doses of captopril greater than 225 mg/d have been associated with agranulocytosis and proteinuria, thought to be related to the sulfhydryl side chain of the drug. The drugs that are highly lipophilic such as quinapril and ramipril bind to ACE in tissue membranes in vitro more avidly than the more hydrophilic agents such as captopril. Although the mechanistic importance of inhibiting angiotensin II formation and facilitating nitric oxide bioavailability in injured tissues such as the heart, kidney, brain, and arteries is undisputed, the clinical significance of tissue ACE inhibition remains unknown. 

There are several pharmacokinetic and pharmacodynamic characteristics of ACEIs with which the clinician should be familiar when prescribing drugs in this class. As mentioned previously, the response of blood pressure to increasing doses of all ACEIs is relative flat whereas the dose-response relationships for other markers of tissue injury such as albuminuria, inflammatory cell activation, and left ventricular hypertrophy are not established clearly. Those drugs that provide 24-hour blood pressure reduction with once-daily dosing are preferred over drugs such as captopril and enalapril, which usually must be taken 2 or 3 times daily to provide similar blood pressure control. Compliance with taking medications that require multiple doses per day is less than with those that can be administered once daily. Drugs that are metabolized by the liver have higher peak plasma concentrations and areas under the curve (AUC) in patients with moderate hepatic cirrhosis; the starting dose of an ACEI in those patients should be reduced and dose increments should be made with careful monitoring of the blood pressure. The same approach applies to administration of ACEIs eliminated predominantly by the kidney for patients with renal impairment, particularly those with glomerular filtration rates less than 30 mL/min. Increases of the serum creatinine level are to be expected in patients with chronic kidney disease, but usually do not exceed 150% of pretreatment values over a 4-week period unless the patient has underlying bilateral renal artery stenosis or stenosis of the renal artery to a single kidney. Therefore, modest changes in the serum creatinine level should not deter the physician from continuing ACEI therapy. Patients who are fluid volume depleted because of diuretic therapy or gastrointestinal fluid loss are often more susceptible to hypotension and ACEI therapy should be initiated with a reduced starting dose. Patients of African descent exhibit a smaller reduction in blood pressure than those of Northern European descent. 

The most irritating but least worrisome adverse effect of ACE inhibitor is nonproductive cough. This adverse effect occurs in 5% to 20% of patients taking ACEIs, is thought to be mediated by bradykinin or substance P, is a class effect and therefore will not likely resolve if one ACEI is substituted for another, and has not been linked to any specific pulmonary functional changes or bronchial reactivity. Although far less frequent but more potentially life-threatening is angioedema. The incidence of angioedema is about 0.3% in large clinical trial populations; is more common in those of African descent; may present initially as minimal to modest swelling of the lips, tongue, and throat, and then becomes more severe over time. It may occur only in the intestine, presenting as intermittent abdominal pain and diarrhea. 

Treatment of women with either ACEIs or ARBs during the second or third trimesters of pregnancy is contraindicated because of the high risk for fetal hypotension, acute renal failure, oligohydramnios, calvarial and pulmonary hypoplasia, and limb deformities, all of which appear to be consequences of maternal/placental hypotension and/or interference with the fetal renin-angiotensin system. 

Recent reports of an increase in cardiovascular events in patients treated with cyclooxygenase-2 inhibitors versus placebo have resulted in valdecoxib being withdrawn from the market. Although the clinical trial in which this outcome was observed was not designed specifically to gather information
about potential mechanisms, studies before the initiation of these trials showed a greater increase in blood pressure with valdecoxib than with celecoxib in hypertensive patients who had stable controlled blood pressure on ACEI therapy. In a more recent investigation it was observed that diclofenac produced a greater increase in the 24-hour mean blood pressure and a greater decrease in glomerular filtration rate than did celecoxib in ACEI-treated African Americans and Hispanics. Collectively, these findings suggest that inhibitors of the cyclooxygenase enzyme either should be avoided or used with caution in hypertensive patients being treated with ACEIs.

**ARBS**

ARBS inhibit the actions of angiotensin II at the tissue level by competing with this potent vasoconstrictor for binding to the angiotensin AT1-subtype receptor, the receptor that mediates the well-documented cardiovascular and renal actions attributed to angiotensin II. Some of these drugs, as the cornerstone of a multidrug therapeutic regimen, have exhibited cardioprotective or renoprotective benefits in patients with a variety of chronic kidney disease or proteinuria. A thorough discussion, however, of these clinical trial results is beyond the scope of this article.

Structural differences in the 7 compounds (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan) currently marketed in the United States likely account for the observed differences in bioavailability, metabolism, potency, and duration of action of these drugs. Despite these differences, the ARBs as a class are well tolerated over a broad range of doses. In blinded, placebo-controlled, clinical trials the reported incidence of adverse effects of these drugs is low and often indistinguishable from those ascribed to placebo.

Each of the 7 drugs in this class marketed in the United States bind to the AT1 receptor with high affinity compared with their binding to other angiotensin receptors. Losartan, valsartan, and eprosartan showed competitive or surmountable receptor binding whereas olmesartan, irbesartan, candesartan, telmisartan, and the major active metabolite of losartan, EXP3174, exhibit noncompetitive or insurmountable binding. Candesartan cilexetil and olmesartan medoxomil are prodrugs that are hydrolyzed to the active moieties by hydrolysis in the gastrointestinal mucosa. Losartan is metabolized extensively in the liver, in part by the cytochrome P450 isoenzymes, 3A4 and 2C9. About 15% of the dose is converted to the more potent EXP3174 metabolite. The duration of action of all of these drugs, or in the case of losartan its active metabolite, is sufficiently long that they maintain 24-hour efficacy when administered once daily. Although the bioavailability of valsartan (40%) and losartan (10%) are reduced if administered with food and the bioavailability of eprosartan (55%) is increased, dosage adjustments almost never are necessary. The drugs in this class generally are well tolerated, in part because they exhibit few interactions with other drugs. Exceptions include losartan, whose half-life is decreased by rifampin and increased by phenytoin, and telmisartan, which may increase digoxin AUC by about 25%. ARBs, such as ACEIs, should not be taken during pregnancy because of the fetopathy caused by interruption of the fetal renin-angiotensin system. The reader is referred to several comprehensive reviews for more detailed information about the pharmacodynamics and pharmacokinetics of the ARBs.

### α1-Adrenergic-Receptor Antagonists

Selective α1-blockers promote vascular smooth muscle relaxation by antagonizing the binding of norepinephrine to the α1-adrenergic receptor in this tissue. Drugs in this class (prazosin, terazosin, and doxazosin) have a similar effect on smooth muscle in the prostate and therefore are indicated for both hypertension and prostatic hypertrophy with symptoms of lower urinary tract outlet obstruction. The principal target population for which monotherapy with these drugs might be considered is elderly men with both hypertension and prostatic hypertrophy. An added benefit of selective α-blocker therapy in older patients at increased risk for coronary artery disease–related events is a modest reduction in low-density lipoprotein cholesterol and triglyceride levels accompanied by a slight increase in high-density lipoprotein cholesterol levels. However, there is concern about an increased incidence of first-dose orthostatic hypotension in this same patient population because older individuals have diminished autonomic nervous system compensatory responses to hypotensive stimuli.

### Other Drugs

#### Direct-Acting Vasodilators

Hydralazine and minoxidil are drugs that act directly on vascular smooth muscle cells to promote vasorelaxation although the cellular mechanisms by which this is accomplished differ. These potent hypotensive agents usually are prescribed as part of a therapeutic regimen for the patient whose hypertension is refractory to multidrug therapy. Hydralazine also has been used effectively as part of a multidrug regimen in the management of heart failure. Recently, hydralazine combined with isosorbide dinitrate has been reported to reduce cardiovascular mortality more than conventional therapy in African Americans with severe heart failure and historically more than the same therapy in Caucasian Americans, although the factors contributing to this ethnic difference have not been defined clearly. Both drugs reduce peripheral resistance and have far less effect on venous capacitance. Decreasing arterial pressure by this mechanism causes reflex activation of the sympathetic nervous system and the renin-angiotensin system, resulting in tachycardia and renal retention of sodium. Consequently, these drugs are given most frequently with diuretics and β-blockers, combined α–β-blockers such as labetalol or carvedilol, or sympatholytic agents such as clonidine or reserpine.
Hydralazine

Hydralazine is a potent vasodilator that can be administered parenterally or orally. The precise intracellular mechanism(s) by which the drug causes smooth muscle cell relaxation is not well established but likely culminates in an inhibition of calcium release from the sarcoplasmic reticulum. The drug is unstable chemically and extensively converted to a variety of metabolites; the relative concentrations of different metabolites are dependent on the subject’s acetylator phenotype. Acetylator phenotype (fast versus slow), however, does not influence substantially the hypotensive response to this drug. A volume of distribution larger than total body water with sequestration of the drug or its active metabolites in tissues probably accounts for the observation that the hypotensive effect of the drug is longer than would be predicted by its elimination half-life of 13 to 125 minutes after oral administration. To maintain 24-hour efficacy during chronic therapy the drug must be administered every 6 to 8 hours. In addition to the pharmacologic adverse effects often associated with vasodilators (flushing, headache, palpitations, arrhythmias, angina pectoris, myocardial infarction, and peripheral edema), the drug produces a lupus-like syndrome in some patients usually after 6 to 24 months of therapy. The interaction of the hydrazine moiety of hydralazine with DNA to interfere with normal DNA methylation has been implicated in this condition, which almost always occurs in slow acetylators and is not predicted by a positive antinuclear antibody (ANA). The incidence of this drug-induced lupus is dose dependent and has been reported to occur in 5.4% of patients receiving 100 mg of hydralazine daily and in 10.4% of those receiving 200 mg daily, with a slightly higher incidence in women than in men. Fortunately, the clinical manifestations of the syndrome (arthritis, glomerulonephritis) resolve when the drug is discontinued.

Minoxidil

Minoxidil activates adenosine triphosphate-sensitive potassium channels, primarily in arterial rather than in venous smooth muscle. Activation of these channels promotes vascular relaxation by inhibiting the entry of calcium into the cell (see Sica and Campese for review). After almost complete absorption by the gastrointestinal tract, the drug is metabolized mainly in the liver. Of the 3 principal metabolites (glucuronide, sulfate, and 4-hydroxy minoxidil), the sulfate is more active than the parent drug whereas the glucuronide and 4-OH metabolites are much less active. Similar to hydralazine, minoxidil has a volume of distribution larger than total body water, is concentrated in tissues, and therefore its biologic effect lasts longer than would be expected from its elimination half-life of 2.8 to 4.2 hours. Although the drug, whose hypotensive effect is related to dose and extent of blood pressure increase, can be administered once daily (usual maintenance dose is 10-40 mg/d), it most often is given twice daily to blunt a significant increase in heart rate that may accompany peak plasma concentrations of the drug. The tachycardia and fluid retention that accompanies minoxidil therapy is even more striking than that observed with hydralazine therapy. Edema and weight gain can be rapid and profound, often necessitating high doses of loop diuretics. Empirically, it has been observed that the addition of metolazone to the loop diuretic may augment the natriuretic response more than further increasing the loop diuretic dose. Fluid can be retained in tissues other than the lower extremities. For example, pericardial effusions can occur rarely and all patients with profound fluid retention on minoxidil should be monitored for this possibility. Minoxidil may cause widespread hypertrichosis of the face, scalp, and body in both women and men, sometimes so emotionally disturbing to the patient that they choose to discontinue the drug. Despite the challenges posed by the use of minoxidil, it is arguably the single most effective antihypertensive agent available for the treatment of resistant hypertension.

Sympatholytic Drugs

Sympatholytic drugs such as clonidine, α-methyldopa, reserpine, and the ganglionic blockers (guanethidine, guanfacine, and guanabenz) are prescribed rarely or not at all as primary therapy for hypertension. They may, however, be used as adjunctive therapy for hypertensive patients who are resistant to therapy with 3 or more drugs from other classes or are intolerant of drugs from other classes.

Combination Drug Therapy

Treatment of Hypertension

Single-drug therapy to control blood pressure likely will be effective in only a minority of hypertensive patients. Based on the experience gained in randomized controlled trials, the JNC 7 report recommends that clinicians consider initiation of therapy with 2 drugs when the blood pressure is 20/10 mm Hg or more above the desired goal. This recommendation would apply to patients with uncomplicated stage II hypertension whose blood pressure is 160/100 mm Hg higher and to those individuals with diabetes or chronic kidney disease whose blood pressure is 150/90 mm Hg because the recommended goal in these patient populations is 130/80 mm Hg.

Decisions about which drugs to combine usually are predicated on the individual patient’s medical profile. Consideration should be given to the patient’s age, race, coexistent cardiovascular and noncardiovascular conditions, and to the extent of blood pressure increase. Socioeconomic issues, the potential for serious adverse effects, and the drugs being used to treat comorbid conditions such as arthritis, gastrointestinal abnormalities, and hematologic disorders are factors that may influence decisions about the most appropriate antihypertensive drugs of a specific patient.

The choice of 2 or more drugs that target different pathophysiologic processes in hypertension and its sequelae often will result in blood pressure control superior to that achieved with single-drug therapy, a benefit that may be achieved with lower doses of each drug and fewer adverse effects. Table 1 summarizes the drugs currently marketed in the United States for the treatment of hypertension that combine agents...
from 2 different drug classes. Figure 2 shows the drugs most frequently prescribed in combination, either as single agents with 2 separate prescriptions or as components of a single pill combination, those that have been shown to have the least additive blood pressure lowering efficacy in clinical trials, and those studied less well or not at all. Because diuretics activate the renin-angiotensin-aldosterone system, it is logical to combine them with classes of drugs that inhibit this potent vasoconstrictor (angiotensin II) and sodium-retaining (aldosterone) system. Combinations of ACEIs or ARBs with diuretics, for instance, provide equivalent blood pressure reduction in African Americans and Caucasians whereas ACEIs or ARBs alone do not.1078 Limited data suggest that cardiovascular event reduction with a β-blocker–based therapeutic regimen may be superior to an ARB-based regimen in African Americans although this possibility has yet to be tested rigorously in an appropriately designed clinical trial.79 An additional benefit of ACEI or ARB plus diuretic combinations is a

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic (thiazide)</td>
<td>Diuretic (K⁺ sparing)</td>
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</tr>
<tr>
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<td>β-blocker</td>
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<tr>
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<td>Vasodilator</td>
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<td>Diuretic (thiazide)</td>
<td>ACEI</td>
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<td>Diuretic (thiazide)</td>
<td>ARB</td>
<td>7</td>
</tr>
<tr>
<td>Diuretic (thiazide)</td>
<td>DCA or NDCA</td>
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</tr>
<tr>
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<td>α₁ antagonist</td>
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</tr>
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<tr>
<td>ACEI</td>
<td>ARB</td>
<td>0</td>
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</tbody>
</table>

Data from the Physician’s Desk Reference.91

Figure 2 This figure depicts possible combinations of drugs from two drug classes that could be used to treat hypertensive patients requiring at least two drugs for control of elevated blood pressure. Drug classes connected by solid arrows represent those combinations for which there is clinical trial evidence of superior efficacy, reduced adverse events, or both compared to monotherapy. Fixed doses of the two drugs in a single pill also are available for these combinations. Dashed arrows connect two drug classes for which there is either little or no clinical trial evidence of efficacy or reduced adverse events or for which fixed dose combinations are not available in the United States. Reproduced with permission, Advantage Communications, LLC, 2004.
lower incidence of hypokalemia than with diuretics alone. In fact, the concomitant use of potassium-sparing diuretics such as triamterene, spironolactone, amlodipine, or oral potassium supplementation in patients taking these combinations is discouraged in most because of the risk for hyperkalemia. 

Diuretics often are combined with direct-acting vasodilators such as hydralazine and minoxidil because of the peripheral edema that may develop when unopposed reflex activation of the sympathetic nervous system by drugs in this class results in increased renal sodium reabsorption. Frequently a third drug, a β-blocker or a central sympatholytic agent such as clonidine, is added to blunt the reflex tachycardia consequent to sympathetic activation.

Combinations of calcium antagonists and ACEIs have been studied extensively in randomized clinical trials. A fixed-dose combination of amlodipine/benazepril, 10/20 mg, controlled blood pressure in a greater percentage of patients with stage II hypertension (61%) than did amlodipine alone at 10 mg (43%); the incidence of peripheral edema in patients taking the combination was half that of patients on amlodipine monotherapy. In another study, patients with systolic hypertension achieved better blood pressure reduction on amlodipine/benazepril 5/20 mg than patients receiving either amlodipine 10 mg or benazepril 40 mg. Low fixed-dose amlodipine/benazepril also has been shown to improve arterial distensibility and reduce left ventricular mass in hypertensive patients more than higher doses of either drug given as monotherapy. Even though DCAs such as amlodipine given as monotherapy either have no effect or worsen urinary protein excretion in patients with proteinuria, they do not negate the reduction in proteinuria observed with ACEIs when administered as part of an ACEI-DCA combination, probably because both systemic blood pressure and intraglomerular pressure are reduced by the complementary action of the 2 drugs on the afferent and efferent arteriole, respectively. The NDCA drugs such as verapamil have either a neutral or less-negative effect on proteinuria than the DCAs and actually may improve urinary protein excretion when given with an ACEI. The pre-capillary arteriolar and post-capillary venular dilating effects of DCAs and ACEIs, respectively, balance pressure across the capillary which results in a reduction of the peripheral edema associated with DCA monotherapy in some patients.

The effects of combining ARBs with CCBs on renal function, proteinuria, surrogate markers of cardiovascular disease such as left ventricular mass or arterial distensibility, and CCB-associated adverse effects have not been studied systematically to date. Therefore, it is not surprising that fixed-dose combinations of drugs representing these 2 classes are not available. Also absent from the list of fixed-dose combinations are drugs containing both an ACEI and an ARB. Interest in conducting studies to obtain Food and Drug Administration approval for such combinations likely will increase if pilot trials of such combinations show a more marked reduction in the rate of deterioration in renal function in diabetic and hypertensive patients than is achieved with either ACEIs or ARBs alone.

The addition of drugs to the patient’s therapeutic regimen to achieve goal blood pressure other than those combinations included in Figure 2 sometimes is necessary. In selected patients, especially those with evidence of increased sympathetic nervous system activity, α1-receptor antagonists and sympatholytic agents including clonidine and reserpine may be indicated. In the patient whose blood pressure still is increased despite 3-drug therapy (defined as resistant hypertension by JNC 7), the addition of low-dose spironolactone should be considered. An additional mean blood pressure reduction of 25/12 mm Hg was achieved in both African-American and Caucasian resistant hypertensive patients taking calcium antagonists, ACEIs, and diuretics 6 months after adding spironolactone to this regimen in doses titrated up to 50 mg. The response to spironolactone was similar in those patients with and without evidence of hyperaldosteronism.

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