SEMINARS IN
NEPHROLOGY

Clinical Pharmacology of Antihypertensive Therapy

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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.

KEYWORDS antihypertensive drugs, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel antagonists, beta blockers, diuretics, alpha-1 adrenergic blockers, combination therapy

Uncontrolled hypertension is the most common treatable cause of cardiovascular and renal morbidity and mortality. There currently are more than 200 different drugs approved by the US Food and Drug Administration that are available to physicians in the United States to treat hypertensive patients. Despite the introduction of newer drugs that not only reduce cardiovascular mortality and morbidity but do so with fewer adverse effects than older antihypertensive agents, blood pressure is controlled to levels currently recommended by the most recent national guidelines in only one third of patients with hypertension.[1]

Numerous clinical trials have documented that 2 or more drugs are needed to control blood pressure in a majority of patients. One additional lesson learned from the Antihypertensive Lipid Lowering Heart Attack Trial[2] (ALLHAT) was that even though blood pressure may be controlled initially on a single antihypertensive medication, additional medications may need to be added over time to maintain goal blood pressure values.[3] In the ALLHAT trial about 70% of patients had achieved goal blood pressure values 6 months after randomization to single-drug therapy. After 5 years of follow-up evaluation, however, only about 30% of patients remained controlled on monotherapy and 70% required 2 or more drugs. Physicians often are reluctant to add medications to a patient's therapeutic regimen for a variety of reasons. In addition, a large minority of patients do not take their medications as prescribed because of cost, adverse effects, social stigmata, or other reasons. Thus, primary care physicians and specialists alike must be familiar with both the actions and the adverse effects of antihypertensive drug classes so they can treat patients with the most therapeutically and cost-effective drugs or drug combinations while minimizing adverse effects that may precipitate discontinuation of therapy by the patient. This article reviews the pharmacologic actions and adverse effects of the most commonly prescribed drugs for the treatment of hypertension in the outpatient setting. A working knowledge of this information allows clinicians to make rational choices of drugs or drug combinations both for treatment of the uncomplicated hypertensive patient and for subgroups of the hypertensive population who pose unique challenges such as African Americans, the elderly, diabetics,

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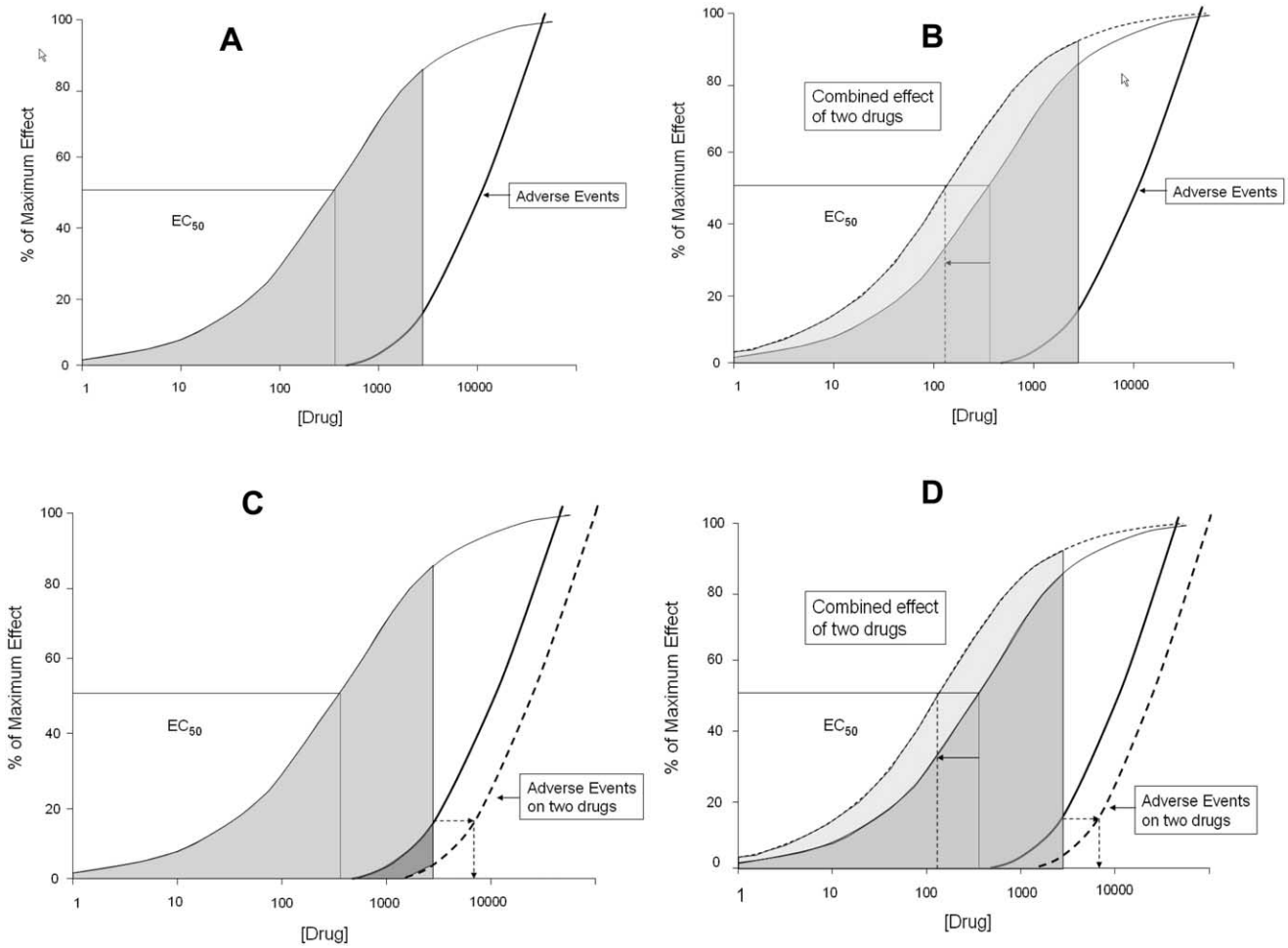

Figure 1 Panel A depicts a typical sigmoid dose-response relationship between [Drug] concentration on the x-axis and the % of maximum drug effect on the y-axis. The dose of drug which elicits 50% of the maximum effect (EC_{50}) is illustrated by the horizontal line. Adverse events (solid black line) typically are either absent or of low incidence until the drug dose is increased to well above the EC_{50}. For this reason, it is preferable to avoid using doses of drug which are near the maximum effect.

Panel B illustrates the effect on the EC_{50} when a second drug is added to the first (light and dark gray areas). The effectiveness of the drug combination compared to that of a single drug (dark gray) is increased by using low doses of two drugs with little effect on the incidence of adverse events.

Panel C illustrates an effect of reducing the dose-dependent incidence of adverse events attributable to the first drug by adding a second drug which reduces the adverse events caused by the first drug.

Panel D illustrates the effect of using two drugs that, when combined, have not only greater efficacy but also a reduced incidence of adverse events.

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_{50}. The EC_{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.[4,5] 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.[6] 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,[7,8] particularly if they had electrocardiographic abnormalities at entry into the trial.[9]

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.[10] 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.[11,12] 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.[3,13]

Diuretics

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.[14] 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.[8,15]

Although these agents are being recommended by some as initial therapy for all uncomplicated hypertensive patients,[1,2,16] 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.[17] 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.[18] As noted earlier, adverse effects can be minimized by treating with low 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 Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE) trial study suggested that 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.[19]

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.[2] 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[20] 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.[21]

The similarities and differences between chlorthalidone and hydrochlorothiazide have received considerable attention recently[22] 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.[2] 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 β_1 versus β_2 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 carvediolol 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 β_1 than β_2 receptors and are referred to as *cardioselective*. This term, however, is relative because the blockade of both β_1 and β_2 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.[23,24]

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 β_2-receptor–mediated reduction in renin release

with consequent reduction in angiotensin II concentrations. A sympatholytic effect also occurs by blocking β_2-receptor–mediated increases in norepinephrine release from sympathetic nerve terminals. These mechanisms of action have implications for the effectiveness of β-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 β-blockers reduce blood pressure much less in this ethnic group than in Caucasian hypertensive patients.[25] African Americans with heart failure, however, experience the same reduction in mortality and morbidity with β-blockers as do Caucasian patients.[26] The elderly tend not only to have a higher incidence of low-renin hypertension than younger individuals but also to exhibit blunted β-receptor–mediated responses to β-agonists.[27] These differences may explain why the elderly derive less survival benefit from β-blockers than do their younger counterparts.[28]

A concern has been expressed in the literature about using β-blockers in patients with cardiovascular disease who have concomitant reactive airway disease. β-blockers, especially those with a high affinity for the β_2 receptor, are relatively contraindicated in patients with asthma and chronic lung disease with a significant bronchospastic component.[29] The results of a recent meta-analysis of studies that have explored the use of cardioselective β-blockers in these patients suggest that cardioselective β-blockers not only are safe but actually may enhance sensitivity to inhaled β-agonists because of receptor activation.[30,31]

Although β-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.[32] 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 β-blockers is unclear. Nevertheless, this provocative re-appraisal of atenolol casts doubt on the relative use of β-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 in Hypertension (LIFE) study.[33] In this trial, losartan-based treatment 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 β-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 α_{1c} subunit of the L-type calcium channel,[34] suggesting that they could have complementary effects when given together in a clinical setting.[35] 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.[36]

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.[37,38] This amlodipine enantiomer also potentiates the nitric oxide synthase–stimulatory effect of the ACEI, ramiprilat.[39] 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.[40]

ACEIs

Since captopril, the first orally active nonpeptide inhibitor of ACEIs, 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 Cushman[41] 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.[42]

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,[43] 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.[44]

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.[45] 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[46] 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.[47]

The most irritating but least worrisome adverse effect of ACE inhibitor is nonproductive cough.[48] This adverse effect occurs in 5% to 20% of patients taking ACEIs, is thought to be mediated by bradykinin or substance P,[49] 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.[50] Although far less frequent but more potentially life-threatening is angioedema. The incidence of angioedema is about 0.3% in large clinical trial populations[51]; is more common in those of African descent[51,52]; 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.[53]

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.[54,55]

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.[56] 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.[57] 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 AT_1-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.[58,59] 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 AT_1 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 cilexitil 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,[58] and telmisartan, which may increase digoxin AUC by about 25%.[60] 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.[58,59,61,62]

α_1-Adrenergic–Receptor Antagonists

Selective α_1-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.[63] 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.[64] 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.[65]

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.[66] 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[67] and historically more than the same therapy in Caucasian Americans,[68] 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.[69] Consequently, these drugs are given most frequently with diuretics and β-blockers, combined α–β-blockers such as labetalol or carvediolol, or sympatholytic agents such as clonidine or reserpine.[70,71]

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.[72] 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.[73] 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.[69] 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,[74] which almost always occurs in slow acetylators and is not predicted by a positive antinuclear antibody (ANA).[69] 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.[75] Fortunately, the clinical manifestations of the syndrome (arthralgias, 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[66] and Campese[76] 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.[77] 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.[76] 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 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.[1] This recommendation would apply to patients with uncomplicated stage II hypertension whose blood pressure is 160/100 mm Hg or 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.[2,10,78] 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 1 Fixed-Dose Combination Drugs Marketed for Hypertension and other Cardiovascular Disorders

Drug 1	Drug 2	Number
Diuretic (thiazide)	Diuretic (K^+ sparing)	4
Diuretic (thiazide)	β-blocker	10
Diuretic (thiazide)	Vasodilator	1
Diuretic (thiazide)	ACEI	8
Diuretic (thiazide)	ARB	7
Diuretic (thiazide)	DCA or NDCA	0
Diuretic (thiazide)	α_1 antagonist	0
Diuretic (thiazide)	α_2 agonist	1
NDCA	ACEI	1
DCA	ACEI	2
ACEI	ARB	0

Data from the Physician's Desk Reference.[91]

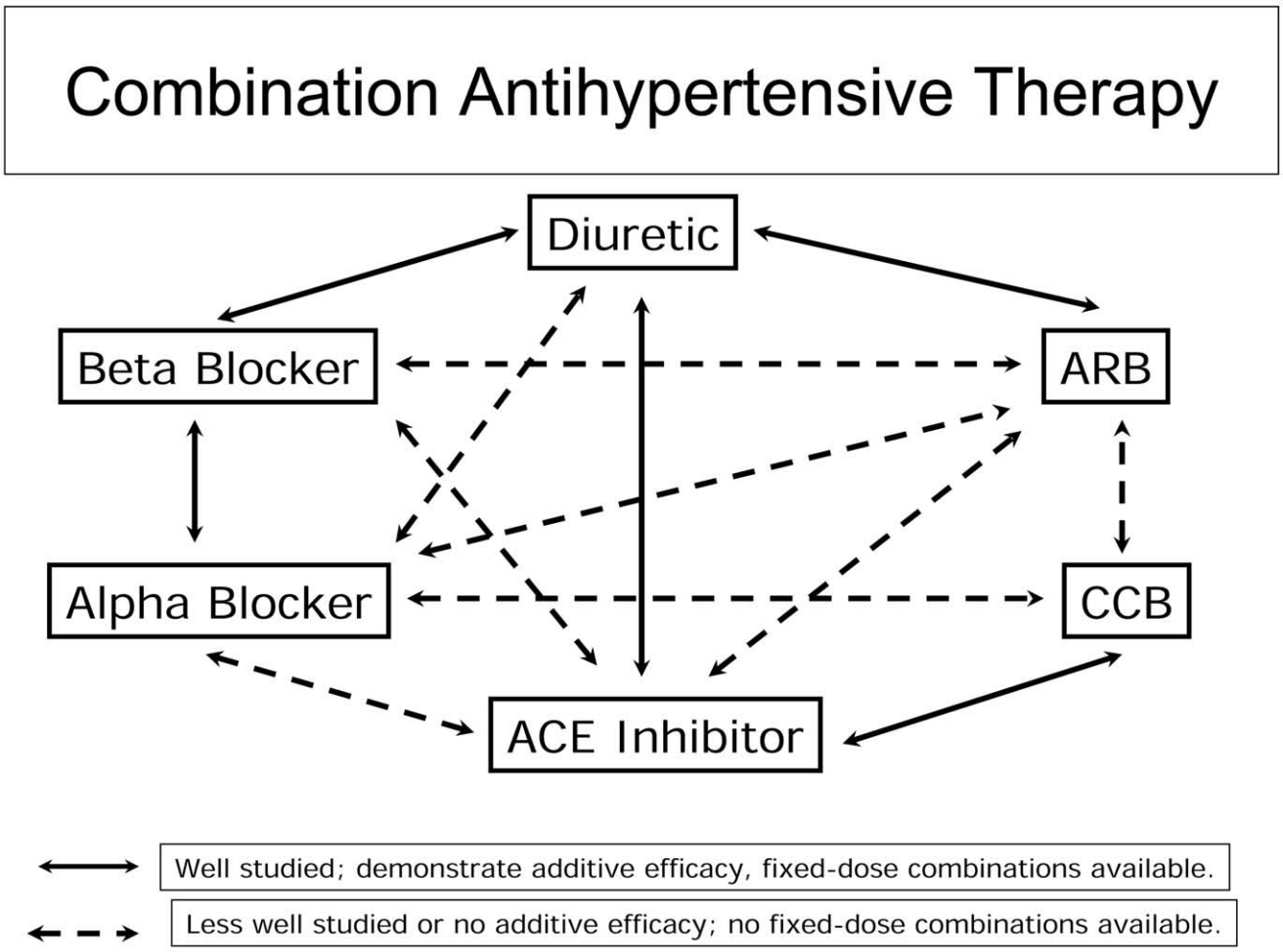

Figure 2 This figure depicts possible combinations of drugs from two drug classes that could be used to treat hypertensive patients requiring at least two drugs for control of elevated blood pressure. Drug classes connected by solid arrows represent those combinations for which there is clinical trial 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 triameterene, spironolactone, amiloride, or oral potassium supplementation in patients taking these combinations is discouraged in most because of the risk for hyperkalemia.[45,80] 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.[66] 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.[66]

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.[81] 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.[82] 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.[83] Even though DCAs such as amlodipine given as monotherapy either have no effect or worsen urinary protein excretion in patients with proteinuria,[84,85] they do not negate the reduction in proteinuria observed with ACEIs when administered as part of an ACEI-DCA combination,[86] 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.[87] 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.[88] 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.[89]

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, α_1-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[1]), 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.[90] The response to spironolactone was similar in those patients with and without evidence of hyperaldosteronism.

References

1. Chobanian A, Bakris GL, Black HR, et al: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. JAMA 289:2560-2572, 2003
2. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 288:2981-2997, 2002
3. Cushman WC, Ford CE, Cutler JA, et al: Success and predictors of blood pressure control in diverse North American settings: The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). J Clin Hypertens (Greenwich) 4:393-404, 2002
4. De Jong PE, Navis G, de ZD: Renoprotective therapy: Titration against urinary protein excretion. Lancet 354:352-353, 1999
5. Weinberg MS, Kaperonis N, Bakris GL: How high should an ACE inhibitor or angiotensin receptor blocker be dosed in patients with diabetic nephropathy? Curr Hypertens Rep 5:418-425, 2003
6. Morledge JH, Ettinger B, Aranda J, et al: Isolated systolic hypertension in the elderly. A placebo-controlled, dose-response evaluation of chlorthalidone. J Am Geriatr Soc 34:199-206, 1986
7. Franse LV, Pahor M, Di BM, et al: Hypokalemia associated with diuretic use and cardiovascular events in the Systolic Hypertension in the Elderly Program. Hypertension 35:1025-1030, 2000
8. Psaty BM, Smith NL, Siscovick DS, et al: Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. JAMA 277:739-745, 1997
9. Franse LV, Pahor M, Di Bari M, et al: Hypokalemia associated with diuretic use and cardiovascular events in the Systolic Hypertension in the Elderly Program. Hypertension 35:1025-1030, 2000
10. Flack JM, Saunders E, Gradman A, et al: Antihypertensive efficacy and safety of losartan alone and in combination with hydrochlorothiazide in adult African Americans with mild to moderate hypertension. Clin Ther 23:1193-1208, 2001
11. Materson BJ, Reda DJ, Cushman WC, et al: Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. N Engl J Med 328:914-921, 1993
12. Materson BJ, Reda DJ, Cushman WC: Department of Veterans Affairs single-drug therapy of hypertension study. Revised figures and new data. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Am J Hypertens 8:189-192, 1995
13. Materson BJ, Reda DJ, Preston RA, et al: Response to a second single antihypertensive agent used as monotherapy for hypertension after failure of the initial drug. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Arch Intern Med 155:1757-1762, 1995
14. Tarazi RC, Dustan HP, Frohlich ED: Long-term thiazide therapy in

essential hypertension: Evidence for persistent alteration in plasma volume and renin activity. Circulation 41:709-717, 1970
15. Psaty BM, Lumley T, Furberg CD, et al: Health outcomes associated with various antihypertensive therapies used as first-line agents: A network meta-analysis. JAMA 289:2534-2544, 2003
16. Vidt DG: The ALLHAT Trial. Diuretics are still the preferred initial drugs for high blood pressure. Cleve Clin J Med 70:263-269, 2003
17. Pollare T, Lithell H, Berne C: A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. N Engl J Med 321:868-873, 1989
18. Cardinal H, Monfared AA, Dorais M, et al: A comparison between persistence to therapy in ALLHAT and in everyday clinical practice: A generalizability issue. Can J Cardiol 20:417-421, 2004
19. Lindholm LH, Persson M, Alaupovic P, et al: Metabolic outcome during 1 year in newly detected hypertensives: Results of the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE study). J Hypertens 21:1563-1574, 2003
20. Verdecchia P, Reboldi G, Angeli F, et al: Adverse prognostic significance of new diabetes in treated hypertensive subjects. Hypertension 43:963-969, 2004
21. Sica DA: Current concepts of pharmacotherapy in hypertension: Diuretic-related side effects: Development and treatment. J Clin Hypertens (Greenwich) 6:532-540, 2004
22. Carter BL, Ernst ME, Cohen JD: Hydrochlorothiazide versus chlorthalidone: Evidence supporting their interchangeability. Hypertension 43: 4-9, 2004
23. Soriano JB, Hoes AW, Meems L, et al: Increased survival with beta-blockers: Importance of ancillary properties. Prog Cardiovasc Dis 39: 445-456, 1997
24. Freemantle N, Cleland J, Young P, et al: Beta blockade after myocardial infarction: Systematic review and meta regression analysis. BMJ 318: 1730-1737, 1999
25. Brewster LM, van Montfrans GA, Kleijnen J: Systematic review: Antihypertensive drug therapy in black patients. Ann Intern Med 141:614-627, 2004
26. Yancy CW, Laskar S, Eichhorn E: The use of beta-adrenergic receptor antagonists in the treatment of African Americans with heart failure. Congest Heart Fail 10:34-37, 2004
27. Grossman E, Messerli FH: Why beta-blockers are not cardioprotective in elderly patients with hypertension. Curr Cardiol Rep 4:468-473, 2002
28. Messerli FH, Grossman E, Goldbourt U: Are beta-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. JAMA 279:1903-1907, 1998
29. Cazzola M, Noschese P, D'Amato G, et al: The pharmacologic treatment of uncomplicated arterial hypertension in patients with airway dysfunction. Chest 121:230-241, 2002
30. Salpeter SR, Ormiston TM, Salpeter EE: Cardioselective {beta}-blockers in patients with reactive airway disease: A meta-analysis. Ann Intern Med 137:715-725, 2002
31. Ormiston TM, Salpeter SR: Beta-blocker use in patients with congestive heart failure and concomitant obstructive airway disease: Moving from myth to evidence-based practice. Heart Fail Monit 4:45-54, 2003
32. Carlberg B, Samuelsson O, Lindholm LH: Atenolol in hypertension: Is it a wise choice? Lancet 364:1684-1689, 2004
33. Kizer JR, Dahlof B, Kjeldsen SE, et al: Stroke reduction in hypertensive adults with cardiac hypertrophy randomized to losartan versus atenolol: The Losartan Intervention For Endpoint reduction in hypertension study. Hypertension 45:46-52, 2005
34. Hockerman GH, Peterson BZ, Johnson AB, et al: Molecular determinants of drug binding and action on L-type calcium channels. Ann Rev Pharmacol Toxicol 37:361-396, 1997
35. Saseen JJ, Carter BL, Brown TE, et al: Comparison of nifedipine alone and with diltiazem or verapamil in hypertension. Hypertension 28: 109-114, 1996
36. Held PH, Yusuf S, Furberg CD: Calcium channel blockers in acute myocardial infarction and unstable angina: An overview. BMJ 299: 1187-1192, 1989
37. Zhang X, Hintze TH: Amlodipine releases nitric oxide from canine coronary microvessels: An unexpected mechanism of action of a calcium channel-blocking agent. Circulation 97:576-580, 1998
38. Zhang XP, Loke KE, Mital S, et al: Paradoxical release of nitric oxide by an L-type calcium channel antagonist, the R+ enantiomer of amlodipine. J Cardiovasc Pharmacol 39:208-214, 2002
39. Zhang X, Xu X, Nasjletti A, et al: Amlodipine enhances NO production induced by an ACE inhibitor through a kinin-mediated mechanism in canine coronary microvessels. J Cardiovasc Pharmacol 35:195-202, 2000
40. Abernethy DR, Schwartz JB: Calcium-antagonist drugs. N Engl J Med 341:1447-1457, 1999
41. Cushman WC: Are there benefits to specific antihypertensive drug therapy? Am J Hypertens 16:31S-35S, 2003
42. Cai H, Harrison DG: Endothelial dysfunction in cardiovascular diseases: The role of oxidant stress. Circ Res 87:840-844, 2000
43. Irvin JD, Viau JM: Safety profiles of the angiotensin converting enzyme inhibitors captopril and enalapril. Am J Med 81:46-50, 1986
44. Dzau VJ, Bernstein K, Celermajer D, et al: Pathophysiologic and therapeutic importance of tissue ACE: A consensus report. Cardiovasc Drugs Ther 16:149-160, 2002
45. Elliott WJ: Optimizing medication adherence in older persons with hypertension. Int Urol Nephrol 35:557-562, 2003
46. Bakris GL, Weir MR: Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: Is this a cause for concern? Arch Intern Med 160:685-693, 2000
47. Ferdinand KC: Recommendations for the management of special populations: Racial and ethnic populations. Am J Hypertens 16:50S-54S, 2003
48. Israili ZH, Hall WD: Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. Ann Intern Med 117:234-242, 1992
49. Trifilieff A, Da Silva A, Gies JP: Kinins and respiratory tract diseases. Eur Respir J 6:567-587, 1993
50. Boulet LP, Milot J, Lampron N, et al: Pulmonary function and airway responsiveness during long-term therapy with captopril. JAMA 261: 413-416, 1989
51. Gibbs CR, Lip GY, Beevers DG: Angioedema due to ACE inhibitors: Increased risk in patients of African origin. Br J Clin Pharmacol 48:861-865, 1999
52. Brown NJ, Ray WA, Snowden M, et al: Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. Clin Pharmacol Ther 60:8-13, 1996
53. Gregory KW, Davis RC: Images in clinical medicine. Angioedema of the intestine. N Engl J Med 334:1641, 1996
54. Pryde PG, Sedman AB, Nugent CE, et al: Angiotensin-converting enzyme inhibitor fetopathy. J Am Soc Nephrol 3:1575-1582, 1993
55. Lambot MA, Vermeylen D, Noel JC: Angiotensin-II-receptor inhibitors in pregnancy. Lancet 357:1619-1620, 2001
56. White WB, Kent J, Taylor A, et al: Effects of celecoxib on ambulatory blood pressure in hypertensive patients on ACE inhibitors. Hypertension 39:929-934, 2002
57. Izhar M, Alausa T, Folker A, et al: Effects of COX inhibition on blood pressure and kidney function in ACE inhibitor-treated blacks and Hispanics. Hypertension 43:573-577, 2004
58. Israili ZH: Clinical pharmacokinetics of angiotensin II (AT1) receptor blockers in hypertension. J Hum Hypertens 14:S73-S86, 2000 (suppl 1)
59. Oparil S: Newly emerging pharmacologic differences in angiotensin II receptor blockers. Am J Hypertens 13:18S-24S, 2000
60. Stangier J, Su CA, Hendriks MG, et al: The effect of telmisartan on the steady-state pharmacokinetics of digoxin in healthy male volunteers. J Clin Pharmacol 40:1373-1379, 2000
61. Gardner SF, Franks AM: Olmesartan medoxomil: The seventh angiotensin receptor antagonist. Ann Pharmacother 37:99-105, 2003
62. Sica DA, Gehr TW: The pharmacokinetics and pharmacodynamics of angiotensin-receptor blockers in end-stage renal disease. J Renin Angiotensin Aldosterone Syst 3:247-254, 2002
63. Pool JL: Doxazosin: A new approach to hypertension and benign prostatic hyperplasia. Br J Clin Pract 50:154-163, 1996
64. Pool JL, Taylor AA, Nelson EB: Review of the effects of doxazosin, a new

selective alpha 1-adrenergic inhibitor, on lipoproteins in patients with essential hypertension. Am J Med 87:57S-61S, 1989
65. McInnes GT: The value of alpha-blockers in the management of hypertension: A practical view. J Hum Hypertens 5:313-316, 1991
66. Sica DA: Minoxidil: An underused vasodilator for resistant or severe hypertension. J Clin Hypertens (Greenwich) 6:283-287, 2004
67. Taylor AL, Ziesche S, Yancy C, et al: Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 351: 2049-2057, 2004
68. Carson P, Ziesche S, Johnson G, et al: Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. Vasodilator-Heart Failure Trial Study Group. J Card Fail 5:178-187, 1999
69. Reece PA, Zacest R: Hydralazine, in Messerli FH (ed): Cardiovascular Drug Therapy. Philadelphia, WB Saunders, 1990, pp 834-848
70. Sica DA, Gehr TW: Direct vasodilators and their role in hypertension management: Minoxidil. J Clin Hypertens (Greenwich) 3:110-114, 2001
71. Ausubel H, Levine ML: Treatment of hypertension with Ser-Ap-Es. Curr Ther Res Clin Exp 9:29-35, 1967
72. Ellershaw DC, Gurney AM: Mechanisms of hydralazine induced vasodilation in rabbit aorta and pulmonary artery. Br J Pharmacol 134:621-631, 2001
73. Schwartz GL, Turner ST: Pharmacogenetics of antihypertensive drug responses. Am J Pharmacogenomics 4:151-160, 2004
74. Oelke K, Richardson B: Decreased T cell ERK pathway signaling may contribute to the development of lupus through effects on DNA methylation and gene expression. Int Rev Immunol 23:315-331, 2004
75. Cameron HA, Ramsay LE: The lupus syndrome induced by hydralazine: A common complication with low dose treatment. BMJ 289:410-412, 1984
76. Campese VM: Minoxidil, in Messerli FH (ed): Cardiovascular Drug Therapy. Philadelphia, WB Saunders, 1990, pp 849-860
77. Parish JL, Hughes MA, Cherry GW, et al: The effect of minoxidil analogues and metabolites on the contraction of collagen lattices by human skin fibroblasts. Br J Plast Surg 48:154-160, 1995
78. Holland OB, von KL, Campbell WB, et al: Synergistic effect of captopril with hydrochlorothiazide for the treatment of low-renin hypertensive black patients. Hypertension 5:235-239, 1983
79. Julius S, Alderman M, Beevers G, et al: Cardiovascular risk reduction in hypertensive black patients with left ventricular hypertrophy: The life study. J Am Coll Cardiol 43:1047-1055, 2004
80. Juurlink DN, Mamdani MM, Lee DS, et al: Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 351:543-551, 2004
81. Jamerson KA, Nwose O, Jean-Louis L, et al: Initial angiotensin-converting enzyme inhibitor/calcium channel blocker combination therapy achieves superior blood pressure control compared with calcium channel blocker monotherapy in patients with stage 2 hypertension. Am J Hypertens 17:495-501, 2004
82. Neutel JM, Smith DHG: Effects of fixed, low-dose combination amlodipine/benazepril therapy vs component monotherapy on systolic blood pressure: Results of the SELECT (systolic evaluation of Lotrel efficacy and comparative therapies) trial. Am J Hypertens 16:196A, 2003
83. Neutel JM, Smith DHG, Weber MA: Effect of antihypertensive monotherapy and combination therapy on arterial distensibility and left ventricular mass. Am J Hypertens 17:37-42, 2004
84. Agodoa LY, Appel L, Bakris GL, et al: Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: A randomized controlled trial. JAMA 285:2719-2728, 2001
85. Wright JT Jr, Bakris GL, Greene T, et al: Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK trial. JAMA 288:2421-2431, 2002
86. Bakris GL, Weir MR, Dequattro V, et al: Effects of an ACE inhibitor/calcium antagonist combination on proteinuria in diabetic nephropathy. Kidney Int 54:1283-1289, 1998
87. Lash JP, Bakris GL: Effects of ACE inhibitors and calcium antagonists alone or combined on progression of diabetic nephropathy. Nephrol Dial Transplant 10:56-62, 1995 (suppl 9)
88. Boero R, Rollino C, Massara C, et al: The verapamil versus amlodipine in nondiabetic nephropathies treated with trandolapril (VVANNTT) study. Am J Kidney Dis 42:67-75, 2003
89. Messerli FH: Vasodilatory edema: A common side effect of antihypertensive therapy. Curr Cardiol Rep 4:479-482, 2002
90. Nishizaka MK, Zaman MA, Calhoun DA: Efficacy of low-dose spironolactone in subjects with resistant hypertension. Am J Hypertens 16: 925-930, 2003
91. Physician's Desk Reference. Montvale, NJ, Thompson PDR, 2005