Choosing Initial Antihypertensive Drug Therapy for the Uncomplicated Hypertensive Patient

Michael A. Moore, MD

Choosing the initial antihypertensive drug for the uncomplicated hypertensive patient is an important and frequent event for the primary care physician. Patients' first experience with antihypertensive drug therapy will likely affect their long-term perception of hypertension treatment. The choice should be made on the basis of sound scientific data and from the patient's perspective and needs. The drug should be taken once a day, should have proven efficacy in hypertension control and cardiovascular morbidity and mortality reduction, and should have as few side effects as possible. Low-dose thiazide diuretics meet this description, although the need to monitor electrolytes may make them less than ideal. The angiotensin II receptor antagonist class, with side-effects similar to those of placebo in controlled trials, is the most attractive from the patient's perspective, although outcome trial data do not yet exist proving that hypertension treatment with angiotensin II receptor antagonists reduces cardiovascular events. The angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, with their low side-effect profiles and unique effects on vascular remodeling, are attractive second choices to combine with a diuretic if needed, although low-dose diuretic/ß blocker combinations have also been shown to lower blood pressure with minimal side effects. At present, ensuring adequate long-term hypertension control is the most important aspect of hypertensive care, and which antihypertensive drug(s) the physician chooses can greatly affect the hypertensive patient's ability to achieve and to maintain long-term blood pressure control. (J Clin Hypertens. 2001;3:37–44)

From the Hypertension Center, Wake Forest University School of Medicine, Winston-Salem, NC
Address for correspondence/reprint requests: Michael Moore, MD, 144 Winston Court, Danville, VA 24541
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Clinical trials utilizing predominantly thiazide diuretics and ß-adrenergic blockers over the past 30 years have demonstrated that reducing the systolic and/or diastolic blood pressure to <140/90 mm Hg will reduce the risk of cardiovascular death from congestive heart failure, stroke, coronary artery disease, and renal failure.[1–6] In addition, the Hypertension Optimal Treatment Trial (HOT)[7] demonstrated that cardiovascular mortality rates could be improved by further reducing the blood pressure in hypertensive and hypertensive diabetic patients to 130/83 mm Hg and to 120/80 mm Hg, respectively.

CURRENT POOR BLOOD PRESSURE CONTROL

Despite numerous clinical trials demonstrating the benefit of treating hypertension, current control rates for hypertension in the United States are poor. Only 27.4% of Americans with high blood pressure are controlled to the Joint National Committee (JNC)-VI recommended goal of <140/90 mm Hg.[1] In the southeastern United States, control rates are even lower.[8] Poor blood pressure control is a major problem within the managed care of hypertension, where congestive heart failure is the most common reason for hospitalization. Since 80% of congestive heart failure is due to uncontrolled hypertension, better long-term hypertension control could reduce the incidence of heart failure and the attendant health care cost.[9] Beginning in 2000, the National Council on Quality Assurance has included hypertension control as an annual measure of care quality in the Health Plan and Employer Data and Information Set (HEDIS).[10]

It is imperative that the antihypertensive regimen selected is one that the patient can adhere to over a long period. To be successful in preventing

the morbid complications of hypertension, a treatment must be chosen that is effective, and that the patient will continue for many years. For a newly diagnosed, 30-year-old hypertensive patient, daily drug treatment will be needed for potentially 40 years or more.

CHOOSING ANTIHYPERTENSIVE DRUG TREATMENT FOR UNCOMPLICATED STAGE 1 HYPERTENSION (140–159/90–99 MM HG)

After an appropriate trial of lifestyle modifications, if the blood pressure has not reached the recommended goal of less than 140/90 mm Hg, antihypertensive drug therapy should be started.[1] The time for lifestyle interventions prior to utilizing specific therapy varies according to risk. High-risk patients should be started on treatment sooner than low-risk individuals. Nine classes of antihypertensive agents have been shown to reduce systemic hypertension compared to placebo treatment, each through a different pharmacologic mechanism.[1] These antihypertensive drugs have resulted from over 40 years of research, seeking to find the ideal antihypertensive drug.

The ideal antihypertensive drug is affordable, is taken once a day, uniformly lowers 24-hour blood pressure, and in clinical trials has been shown to prevent cardiovascular events while lowering blood pressure. The ideal antihypertensive drug's blood pressure reduction efficacy should be enhanced with appropriate weight loss and a sodium-restricted diet, and cause no side effects or laboratory abnormalities. Finally, other drugs should not reduce its antihypertensive effect. Such an ideal drug does not exist yet, but one of the newer classes approaches this pharmacologic ideal.

Which of the nine classes of antihypertensive drugs should be chosen for an otherwise healthy, asymptomatic hypertensive patient? It is of interest that the degree of blood pressure lowering by the more commonly used classes is very similar. (Table I). In comparing the cost of the various antihypertensive classes, the average wholesale price (AWP) for 100 doses is most useful. Patients can expect to pay the AWP plus a variable mark-up fee and packaging fee. The relative monthly AWP for each class is shown in Table II.[11] Periodic laboratory studies can increase the total cost of a drug class. Based on pharmaceutical sales information from the past several years, clinicians have most commonly chosen a calcium channel blocker, an angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocking drug, a diuretic, or a ß blocker for most hypertensive patients. The JNC-VI has recommended diuretics with ß blockers as initial therapy for uncomplicated hypertensive patients.

Since all of the nine classes of antihypertensive drugs have been shown to lower blood pressure effectively, the clinician should consider five factors in choosing a drug: outcome trial data as to whether the drug has reduced cardiovascular morbidity or mortality, dosing frequency, cost, side effects, and any added benefit beyond blood pressure reduction.

TABLE I. AVERAGE BLOOD PRESSURE REDUCTION AFTER 48 MONTHS OF TREATMENT OF STAGE 1 HYPERTENSION IN THE TREATMENT OF MILD HYPERTENSION TRIAL

	SYSTOLIC	DIASTOLIC
Acebutolol	-13.9	-11.5
Amlodipine	-14.1	-12.2
Chlorthalidone	-14.6	-11.1
Doxazosin	-13.4	-11.2
Enalapril	-11.3	-9.7

Values are mm Hg.
Neaton, JD, Grimm, RH, Pineas, RJ, et al. Treatment of mild hypertension study. *JAMA*. 1993;270:713–724.

EFFECTIVE DRUGS WITH LIMITED USE AS FIRST-STEP ANTIHYPERTENSIVE AGENTS

Sympatholytics and Vasodilators

Sympatholytics and vasodilators are available generically and are relatively inexpensive. Reserpine or α-methyl DOPA in combination with a thiazide diuretic was used in many early clinical trials. These studies demonstrated a reduction in cardiovascular death from coronary artery disease, stroke, and congestive heart failure with treatment of hypertension.[12–16]

All sympatholytics, except reserpine, must be given more than once a day. These agents, including reserpine, α-methyl DOPA, clonidine, and guanabenz, usually require a concomitant diuretic to maintain long-term efficacy, and they have more troubling side effects than newer antihypertensive drugs. Lassitude, mental slowness, nasal congestion, and peptic ulceration can occur with reserpine, particularly in doses greater than 0.25 mg daily. These same mental symptoms plus abnormal liver function can occur with α-methyl DOPA, requiring periodic hepatic function studies. Dry mouth, sedation, and potential hypertensive rebound following drug withdrawal can occur with clonidine and guanabenz.[17]

Hydralazine, in combination with hydrochlorothiazide and reserpine, (Ser-Ap-Es®) was

used in the first hypertension treatment outcome trials, the Veterans Cooperative Studies, which demonstrated that antihypertensive control would reduce death from congestive heart failure and stroke.[13] To maintain and enhance antihypertensive efficacy, the vasodilators hydralazine and minoxidil require a concomitant diuretic and a ß blocker to prevent fluid retention and reflex tachycardia.[18] Among antihypertensive drugs, hydralazine has not been shown to reverse LVH.[1]

Minoxidil is typically reserved for more severe hypertension. Minoxidil, in combination with a ß blocker and loop diuretic, was used effectively by Spitalewitz et al.[18] to treat Stages II and III hypertension and to slow progressive renal failure in some patients. Palpitations and flushing occur with vasodilators, and hypertrichosis is a predictable side effect of minoxidil in men and women. Both vasodilators must be given twice a day.

As initial antihypertensive agents, sympatholytics and vasodilators are not attractive choices.[1]

α-Adrenergic and α-ß-Adrenergic Antagonists

There are three α-adrenergic antagonists—prazosin, doxazosin, and terazosin—and two α-ß-adrenergic antagonists, labetalol and carvedilol. None of the α-adrenergic blockers has been shown to reduce cardiovascular mortality through blood pressure reduction. In hypertensive patients, doxazosin did not prevent angina, congestive heart failure, and overall cardiovascular mortality as effectively as chlorthalidone in the ongoing Antihypertensive Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT) trial.[20] These negative outcomes caused an early interruption of the ALLHAT doxazosin treatment arm by the study's safety committee.[20]

Carvedilol is an effective antihypertensive agent, and lowers blood pressure to the same degree as labetalol. It has been demonstrated to slow the progression of congestive heart failure, to improve heart failure symptoms, and to reduce mortality and hospitalization for cardiovascular events.[21]

Doxazosin and terazosin are once-a-day drugs, while prazosin, labetalol, and carvedilol must be given twice a day. The three pure α-adrenergic blockers can cause sudden hypotension after the first dose, and patients should be instructed to begin these drugs at bedtime. Weight gain presumed to be related to fluid retention can occur with the α antagonists, which blunts their long term antihypertensive effect.[22]

Labetalol, doxazosin, and terazosin have attractive associated effects for certain patients. Labetalol and carvedilol do not decrease cardiac output, as occurs with ß blockers; they lower peripheral vascular resistance and increase peripheral and renal blood flow. Thus, labetalol causes less fatigue than ß blockers, and the drug may be a good choice for hypertensive patients who exercise regularly or those with peripheral claudication.[23]

Doxazosin and terazosin produce a mild reduction in plasma cholesterol and improve bladder emptying in older men with benign prostatic hypertrophy.[22] The negative results of doxazosin in the ALLHAT trial make it a poor first-step drug.[20] It is not known if this negative outcome is a class effect of α-adrenergic antagonists or is unique to doxazosin.

MOST COMMONLY USED ANTIHYPERTENSIVE MEDICATIONS

Diuretics

Thiazide diuretics, along with ß-adrenergic blocking agents, were recommended in 1977 by the Sixth Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure as being the preferred initial antihypertensive drugs.[1] Thiazides have been used in nearly all hypertension clinical trials as a primary or secondary drug, including the current ALLHAT trial.[20] Indeed, it was thiazides combined with a sympatholytic agent or in some cases a vasodilator in the Veterans Cooperative Trials and HDFP trials that initially demonstrated that diastolic and systolic blood pressure lowering could prevent stroke, congestive heart failure, and coronary artery disease.[12–14] Thiazides and ß-adrenergic blockers were used in the Systolic Hypertension in Elderly People (SHEP) and Swedish Trial in Old Patients with Hypertension (STOP-1) trials. In SHEP, the incidence of congestive heart failure was reduced by 50%, stroke by 35%, and coronary artery disease mortality by 25% in older hypertensive patients with isolated systolic hypertension,[2] while in STOP-1, fatal and nonfatal strokes were reduced by 47% and all cardiovascular mortality by 40%, with a reduction in deaths from congestive heart failure.[3] Therapy with low-dose diuretics—25 mg daily or less of hydrochlorothiazide or its equivalent—has been shown in 18 randomized, placebo-controlled clinical trials to produce a 28% reduction in coronary artery disease mortality.[4]

Hydrochlorothiazide is effective once a day. The frequency of side effects increases with dosage, but blood pressure reduction may not.[25] Maximal blood pressure reduction occurs with 25 mg daily of hydrochlorothiazide.[26] Dietary sodium intake restriction increases, while a high salt

diet may minimize, thiazide blood pressure reduction.

The initial daily cost is the lowest of all antihypertensive drugs, but the long-term cost can be higher if hypokalemia develops. Thiazides can cause hypokalemia, hyperuricemia, hypomagnesinemia, and hypercalcemia, but these effects are usually mild and relatively infrequent with small doses.[26] Hypokalemia is more likely to occur with a low potassium/high sodium diet, and with higher doses of diuretics.[26–28] In SHEP, mild hypokalemia (<3.5 mEq/L) occurred in 7.2% of patients taking chlorthalidone at 1 year compared to 1% in the placebo-treated group. The individuals with hypokalemia at 1 year did not experience the same reductions in cardiovascular events, coronary artery disease, or stroke that were achieved among those without hypokalemia.[29] Serum electrolytes should be measured periodically in thiazide-treated patients, and hypokalemia avoided.

While often touted as a risk of thiazide therapy, the initial mild, transient rise in serum cholesterol is not a long-term effect.[25,27] Low-dose (25 mg daily) hydrochlorothiazide produces either no or minimal adverse effect on blood glucose in diabetic patients.[25] The renal calcium-retaining effect of thiazides can be beneficial in preventing recurrent calcium oxalate renal stones and preventing osteoporosis.[1]

Side effects occur in a dose-dependent fashion and may include muscle cramps, weakness, fatigue, photosensitive dermatitis, and impotence. In the HAPPY trial,[30] at 12 months, 16% of patients taking 50 mg of hydrochlorothiazide or 5 mg of bendroflumethiazide reported one or more side effects. Impotence was reported by 22.6% of men taking bendrofluazide compared to 13.2% of men taking placebo after 2 years in the Medical Research Council (MRC) trial.[31] At 48 months, 16.5% of men in the Treatment of Mild Hypertension Study (TOMHS) taking chlorthalidone, 15 mg daily, reported difficulty maintaining an erection, compared to 13.1% taking placebo ($p<0.02$).[11] At 4 years, there was no statistically significant difference in sexual dysfunction between patients on diuretics, ß blockers, calcium channel blockers, or ACE inhibitors.

ß-Adrenergic Antagonists

ß-adrenergic antagonists (BB), which were used in the HDFP, SHEP, STOP-1, STOP-2, and UKPDS trials, have been shown to reduce cardiovascular deaths through their antihypertensive effect.2,3,14,32 In the SHEP trial, thiazide diuretics with a ß blocker added if necessary reduced death from congestive heart failure, stroke, and myocardial infarction.2 In the two STOP trials, one of three BBs was used. In STOP-1, for those treated with a thiazide diuretic or ß blocker, fatal and nonfatal strokes were reduced by 47%, and all cardiovascular mortality by 40%.3 There was also a reduction in deaths from congestive heart failure. In STOP-2, which involved older patients with stage 2–3 systolic and diastolic hypertension, thiazide diuretics with ß blockers were as effective as an ACE inhibitor or calcium channel blocking drug in reducing fatal strokes, fatal myocardial infarction, and overall cardiovascular mortality.32

With the long-acting ß1-selective agents, such as atenolol and metropolol, once-a-day dosing is standard. The cost of blood pressure control is more than with thiazides but less than with the newer antihypertensive agents (Table II). The BBs have been shown to provide secondary prevention of coronary artery disease by reducing the risk of a second myocardial infarction and sudden death after a first event.[33] However, primary prevention of coronary artery disease in hypertensive patients has been shown in only one of four large clinical trials.[30,34–36] ß Blockade can improve symptoms and slow progression of congestive heart failure.[37] Finally, BBs can reduce plasma renin levels and increase atrial natriuretic factor; the clinical significance of these hormonal effects is not clear.[38]

One added benefit of BBs is the reduction of anxiety related to heightened sympathetic tone. This provides effective therapy of stage fright for actors and musicians.[39] Side effects in uncomplicated hypertensive patients can include fatigue, weakness, insomnia, and reduction in exercise ability.[30,34,40] In the HAPPY trial,[30] at 12 months, 19.1% of participants taking propranolol reported one or more side effects. Mild elevation of triglycerides occurs with some patients on BBs, and the partial blockade of the sympathetic nervous system by BBs minimizes the symptoms of hypoglycemia, requiring caution with their use in diabetic patients at risk of hypoglycemia.[39]

ACE Inhibitors

The first ACE inhibitor was captopril. Initially, it was believed that the blood pressure reduction by ACE inhibitors was due to a reduction in the conversion of angiotensin I to angiotensin II through inhibition of the converting enzyme. While initially, ACE inhibitors reduce plasma angiotensin II levels, more recent research has suggested that the long-term, predominant antihypertensive ACE inhibitor effect may result from the increased bradykinin that results from ACE inhibition of the enzyme kinase II, which is responsible for the degradation of bradykinin.[41] It is now understood that a family of

converting enzymes exists that can produce angiotensin II from angiotensin I throughout the body. Each organ in which angiotensin II has an effect has a converting enzyme.[42] While some of the ACE inhibitors have more effect than others in reducing the activity of the various tissue-converting enzymes, none is believed to block tissue-converting enzyme activity completely.[43] Thus, patients treated with an ACE inhibitor over time may have the same serum angiotensin II levels as before the drug was begun.[44] The net effect of ACE inhibition is to improve vascular endothelial function and to promote healthy vascular remodeling.[45,46]

A series of changes to the original captopril molecule resulted in longer-acting ACE inhibitors, allowing for once-a-day dosing. The ACE inhibitors have been shown in numerous clinical trials to reduce mortality and to improve symptoms from any degree of systolic heart failure and, in combination with other agents, primarily diuretics, to slow progression of hypertensive and diabetic renal disease to end-stage kidney disease.[1,6] In the STOP-2 trial in older patients with systolic and diastolic hypertension,[32] ACE inhibitors and calcium channel blocking drugs were no more effective than thiazides and BBs in reducing fatal strokes, fatal myocardial infarction, and overall cardiovascular mortality.[32] Patients on ACE inhibitors experienced fewer myocardial infarctions or episodes of congestive failure when compared to those on calcium channel blockers. However, there are no outcome trial data to demonstrate that ACE inhibitors, in uncomplicated hypertensive patients, reduce cardiovascular mortality. Side effects are relatively rare compared to all other classes of antihypertensive drugs except for the angiotensin II receptor blocking drugs.

The most common side effect is cough, while the most concerning is angioneurotic edema and hyperkalemia. Hyperkalemia may be seen in some older hypertensive patients and some type II diabetic patients with hyporenin/hypoaldosteronism; this, however, is not a common occurrence.[47] ACE inhibitors should not be used during pregnancy, which limits their use in young, otherwise healthy hypertensive women who might become pregnant.[48]

Angiotensin II Antagonists

The major antihypertensive effect of the angiotensin II receptor antagonists (AIIAs) is through the blockade of tissue receptors for angiotensin II within the vascular bed. They also cause mild natriuresis through blockade of the AT1 receptor on the proximal renal tubule, which modulates sodium reabsorption, and of the AT1 receptors on sympathetic nerves, reducing sympathetic tone in blood vessels.[48] The AIIAs effect blood pressure reduction equal to that of other first step antihypertensive drugs, and they have had almost no side effects in placebo-controlled trials.[49–52] There are no outcome trial data available yet as to whether AIIAs reduce cardiovascular mortality as they reduce blood pressure. The ongoing worldwide Life Trial compares mortality outcome between losartan/hydrochlorothiazde and diuretics/BBs in middle-aged hypertensive patients with left ventricular hypertrophy.[53] Other outcome trials with these agents are underway.

The AIIAs are effective once a day and are priced similarly to other brand name antihypertensive drugs.[54] All of the AIIAs reduce blood pressure to a similar degree.[55] The original AIIA, losartan, has a uricosuric effect and minimizes potassium loss when combined with a diuretic.[56] Valsartan has also been shown to produce the potassium-sparing effect, but among the AIIAs only losartan has a uricosuric effect.[57] The importance of this finding is under study.

Calcium Channel Blockers

Calcium channel blockers (CCB) reduce calcium transport through L-type plasma membrane channels. In smooth muscle cells found within vascular walls, the calcium channel inhibition produces vasodilatation and a reduction in peripheral vascular resistance. The CCBs lower blood pressure as effectively as other classes of antihypertensive drugs; all the longer-acting formulations can be dosed once a day.

There are two major pharmacologic classes of long-acting CCBs.These are the dihydropyridines, such as nefedipine and amlodipine, and the non-dihydropyridines, such as diltiazem and verapamil. The dihydropyridines are more potent vasodilators than the non-dihydropyridines. All CCBs improve coronary artery blood flow and reduce atrial-ventricular conduction to variable degrees.[58] They are useful in hypertensive patients with ischemic heart disease or patients with cyclosporin-induced hypertension.[1] The long-acting dihydropyridine CCBs have been shown to be effective in reducing strokes and overall cardiovascular mortality when used to treat isolated systolic hypertension in the elderly.[5,32,59]

Several years ago, a serious question was raised about short-acting nefedipine increasing cardiovascular mortality.[60] These reports led to short-acting nefedipine no longer being recommended for hypertension treatment. None of the long-acting CCBs was incriminated. There are no long-term outcome trial data in uncomplicated hypertension that long-acting CCBs improve cardiovascular mortality, although the ongoing ALLHAT trial addresses this issue.[23,60]

Side effects are frequent with CCBs, particularly when compared to ACE inhibitors and AIIAs. These include flushing, tachycardia, constipation in older patients, and ankle edema, particularly in women.[39,61] Cost for treatment with the CCBs can be very high, with the brand name CCBs being the most expensive of all the classes of antihypertensive drugs (Table II).

The Ultimate Initial Choice for the Uncomplicated Hypertensive

Since vasodilators require twice-a-day dosing, a concomitant ß-adrenergic antagonist, and, like sympatholytics, a diuretic for sustained efficacy, they are the least attractive choice for the uncomplicated hypertensive patient. The recent concern about the long-term benefit of the α antagonist doxazosin in preventing cardiovascular mortality leaves the clinician choosing among a diuretic, an ACE inhibitor, an AIIA, a BB, or a CCB. The more frequent side effects, lack of outcome trial data on the prevention of cardiovascular mortality in the uncomplicated young hypertensive, and cost make CCBs less attractive than the other four agents. The frequency of side effects from BBs makes them less attractive in the author's experience, despite their outcome trial success, leaving ACE inhibitors, AIIAs, and diuretics. There is no proven benefit of ACE inhibitors in the uncomplicated hypertensive over an AIIA or diuretic. Also, ACE inhibitors produce more side effects than AIIAs.

If outcome trial data were available demonstrating that AIIAs reduce cardiovascular mortality as they control blood pressure, they would be among the preferred drugs for uncomplicated hypertension. The AIIAs are attractive first-step antihypertensive drugs because of their comparable efficacy to other classes of drugs, near absence of side effects, once-a-day dosing, lack of induced laboratory abnormalities, and the blocking of angiotensin II, which is central in the pathophysiology of left ventricular hypertrophy, congestive heart failure, and renal failure. The AIIAs hold the promise that their lack of side effects may provide better long-term patient compliance. However, currently there are no outcome trial data demonstrating that AIIAs can reduce cardiovascular deaths beyond their primary antihypertensive effect.[44,45] Thus, a thiazide diuretic currently remains the most attractive first-step choice for the uncomplicated hypertensive patient due to efficacy, once-a-day dosing, and the large amount of outcome trial data.

TABLE II. AVERAGE WHOLESALE COST (AWP) IN DOLLARS FOR 30 DAYS OF TREATMENT WITH A DRUG FROM EACH ANTIHYPERTENSIVE DRUG CLASS

DRUG	STRENGTH	AWP/100	AWP 30 DAYS
Hydralazine*	25 mg	3.75	2.3
Clonidine*	0.1 mg	2.4	1.4
Hydrochlorothiazide	25 mg	1.49	0.4
Atenolol	50 mg	70.3	21.1
Enalapril	10 mg	110.36	33.1
Verapamil	120 SR generic	29.93	9.0
Amlodipine	5 mg	132.41	39.7
Losartan	50 mg	125.1	37.5
Valsartan**	160 mg	121	42.0

*Twice-a-day dosing required. **Dose equivalent to that of losartan for similar blood pressure reduction. From *Hospital Formulary Pricing Guide*. Indianapolis, IN: Medi-Span, Inc.; 1999.

CHOOSING THE SECOND DRUG FOR UNCOMPLICATED HYPERTENSION

In many cases, one antihypertensive drug will not be adequate to reach the goal blood pressure, even with stage I patients. This will become even more likely if the treatment goal for uncomplicated hypertension is lowered to less than 130/85 mm Hg, as has been recommended by the investigators in the HOT trial.[6]

A fixed combination of various classes of antihypertensive agents is an effective approach to hypertension management. Antihypertensive drug combinations can provide synergistic blood pressure reduction, often with reduced doses, once-a-day dosing of multiple drugs, fewer side effects, and

TABLE III. EXAMPLES OF FIXED COMBINATIONS OF ANTIHYPERTENSIVE DRUGS

ß-Adrenergic blocking drugs and diuretics
Angiotensin II-converting enzyme inhibitors and diuretics
Angiotensin II receptor blocking drug and diuretics
Calcium channel blocking drugs and angiotensin II-converting enzyme inhibitors.

Information obtained from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med*. 1997;157:2413–2446.

often less cost than if the drugs were bought separately.[1] Six classes of antihypertensive agents are available in combinations (Table III).[1]

For stage I hypertensive patients, a diuretic should be one of the drugs in the combination, due to the proven efficacy in blood pressure reduction and cardiovascular mortality prevention. The combination of an AIIA or ACE inhibitor with a diuretic is attractive because of the low frequency of side effects and the synergistic effect on blood pressure reduction. In addition, data suggest that a low-dose combination of a ß blocker/diuretic is effective and well tolerated.

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