Drug Therapy for Hypertension in the Elderly

Evan W. Kligman, MD, and Martin D. Higbee, PharmD
Tucson, Arizona

Essential hypertension is a major health care problem in the elderly and requires effective treatment to reduce morbidity and mortality. The traditional stepped-care approach to therapy consisted of diuretics, sympatholytic agents, or β-blockers for all age groups. Indeed, initial therapy with these agents is effective in 50 to 60 percent of elderly patients but may produce adverse effects. A high incidence of adverse responses, including sexual dysfunction and central nervous system impairment, has been reported with diuretic or β-blocker therapy, and a reduction in several measures of quality of life has been noted during therapy with methyldopa or propranolol.

Administration of an angiotensin-converting enzyme (ACE) inhibitor is as effective as the traditional stepped-care approach without producing the ill effects associated with diuretics, sympatholytics, or β-blockers. The combination of an ACE inhibitor with a diuretic produces additive antihypertensive effects while minimizing diuretic-induced metabolic alterations. Orthostatic hypotension with the first dose can be minimized by making sure that patients are not hypovolemic from previous diuretic therapy. Nevertheless, in controlled trials, the combination of ACE inhibitor and diuretic has been effective in up to 85 percent of patients. In addition, the use of ACE inhibitors may be beneficial in the hypertensive patient with concomitant congestive heart failure. Most important, the patient's quality of life is maintained during therapy with an ACE inhibitor alone or in combination with a diuretic. Thus, an ACE inhibitor plus a diuretic is a valuable alternative to traditional antihypertensive therapy in elderly patients.

Hypertension is a major health care problem for the elderly population and a major risk factor for the development of cerebrovascular and cardiovascular disease.[1] Effective treatment of hypertension is essential to reduce the associated morbidity and mortality. The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure[2] recommended either a diuretic or centrally acting sympatholytic for initial therapy in the elderly. As monotherapy, these agents are effective in 50 to 60 percent of patients.[3] For long-term management of hypertension in elderly patients, however, the use of these agents may be limited by side effects, metabolic effects, metabolic alterations, and impairment of quality of life.

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From the Department of Family and Community Medicine, and the Department of Pharmacy Practice, College of Pharmacy, University of Arizona, Tucson, Arizona. Requests for reprints should be addressed to Dr. Martin D. Higbee, Department of Pharmacy Practice, College of Pharmacy, University of Arizona, Tucson, AZ 85721.

An alternative to traditional therapy for treatment of the elderly hypertensive patient is an angiotensin-converting enzyme (ACE) inhibitor alone or combined with a diuretic. As monotherapy, ACE inhibitors are comparable in efficacy to diuretics and β-blockers for initial management of hypertension. The combination of an ACE inhibitor and a diuretic offers the advantages of increased efficacy, a low incidence of side effects, no metabolic alterations, and minimal effect on the patient's quality of life. In this review, treatment options for the elderly hypertensive patient are discussed, and the advantages of an ACE inhibitor-diuretic combination are contrasted with traditional therapy.

EPIDEMIOLOGY OF HYPERTENSION IN THE ELDERLY

Hypertension is a major cause of morbidity and mortality from heart attacks and stroke and a major contributor to congestive heart failure, peripheral vascular disease, and renal disease. Although younger patients are the focus of

much of the concern over the adverse consequences of hypertension, the incidence of hypertension and, thus, the potential for adverse consequences are as great in the elderly population.

In the elderly patient, the treatment of hypertension with commonly used antihypertensive medications is associated with a high incidence of morbidity from adverse drug reactions, often resulting in hospitalization.[4,5] Thus, it is important to understand three factors when considering whether to initiate treatment for hypertension in the elderly.[6]

First, although the average blood pressure does increase with advancing age, high blood pressure is not normal at any age. Hypertension occurs in Western cultures in approximately 40 percent of individuals 65 years of age and older, whereas in nonindustrialized populations, hypertension is not an inevitable consequence of aging.[7] In epidemiological studies, the average of three blood pressure measurements was greater than 140/90 mmHg (ie, consistent with the diagnosis of hypertension) in 64 percent of patients aged 65 to 74 years.[6] Using this same definition, hypertension was present in 68 percent of patients aged 65 to 74 years who were screened for enrollment in the Systolic Hypertension in the Elderly Program.[8]

Second, hypertension carries with it at least as great a risk for morbidity and mortality in the elderly as in younger patients. Systolic hypertension, however, appears to be a better predictor of cardiovascular morbidity and mortality in the elderly than diastolic hypertension. Results from the Framingham study indicate that the risk of cardiovascular mortality is three times greater in the elderly hypertensive patient than among normotensive patients of the same age.[9] The European Working Party on Hypertension in the Elderly (EWPHE)[10] trials showed that coronary heart disease mortality was strongly associated with increasing systolic hypertension (>160 mmHg).

Third, antihypertensive therapy decreases the risk of cardiovascular and cerebrovascular complications in elderly hypertensive patients as well as in younger patients. In three large prospective trials, cardiovascular and cerebrovascular morbidity and mortality were significantly reduced by treatment of hypertension in elderly patients.[11-14] In the EWPHE trial, mortality in patients with diastolic blood pressures 90 to 119 mmHg and systolic blood pressures 160 to 239 mmHg were reduced by therapy. The number of deaths secondary to cardiovascular events was significantly lower in the treated group until the age of 90 years.[10] Drug therapy is recommended in elderly patients with blood pressures greater than 160/90 mmHg to gain the benefits of decreased morbidity and mortality demonstrated to date. Thus, identifying a safe and effective regimen is as important in the elderly as in the young hypertensive patient.

TRADITIONAL STEPPED-CARE THERAPY FOR HYPERTENSION IN THE ELDERLY

Drug therapy for hypertension in the elderly has traditionally consisted of a diuretic used alone or in combination with a β-blocker or sympatholytic. Support for the approach is based on decades of clinical experience. Although these agents, when used alone, are effective, they exhibit adverse reaction profiles that tend to exert a negative impact on quality of life.

Diuretics

As initial monotherapy, thiazide diuretics are effective in 50 to 60 percent of hypertensive patients, producing a reduction in diastolic blood pressure that averages 13 mmHg.[3] Diuretics are particularly efficacious in patients over 50 years of age and in blacks.

Results from prospective, randomized, controlled studies of elderly hypertensive patients show that their response to diuretic therapy is similar to the response observed in younger patients. In the Hypertension Detection and Follow-up Program (HDFP) study, diuretics were used as initial therapy in the stepped-care group. The greatest reduction in the incidence of stroke (45 percent) occurred in the 60- to 69-year-old age group.[14] Similarly, in the Australian Therapeutic Trial, diuretics were used as the initial therapy. A significant reduction (39 percent) in the rate of death or other cardiovascular events occurred in a subgroup of patients aged 60 to 69 years.[13]

The EWPHE trial was a double-blind, placebo-controlled study in which the efficacy of therapy was evaluated in hypertensive patients over 60 years of age.[15] Therapy was initiated with a thiazide diuretic combined with a potassium-sparing agent. In patients up to age 80 years, cardiovascular and cardiac mortality were significantly reduced, 27 and 38 percent, respectively, in the active treatment groups, and deaths from myocardial infarction were decreased by 60 percent. Those older than 80 years did not show these benefits in this study.

Despite the favorable responses to diuretic therapy, side effects such as dizziness, fatigue, decreased libido and impotence, exacerbation of gout, and leg cramps are common.[16] The perception is that 10 percent of patients require discontinuation of therapy because of adverse effects. In the HDFP study, over 20 percent of patients receiving diuretics discontinued therapy because of side effects that were evaluated to be possibly or probably related to therapy.[17] The most common reasons for discontinuing therapy were sexual dysfunction, gastrointestinal disturbances, dizziness, lethargy, and weakness.

In the Medical Research Council (MRC) trial, 17 percent of men and 13 percent of women treated with a diuretic were withdrawn from therapy during a five-year

follow-up of treatment-related side effects.[18] Overall, the incidence of glucose intolerance, lethargy, constipation, dizziness, headache, and nausea were higher in the diuretic group than in the placebo group. The higher incidence of discontinuation in men was attributed to a higher frequency of impotence and gout in this group.

Diuretic-induced metabolic abnormalities have potentially serious implications during long-term use. Diuretics reduce serum potassium concentrations by 0.5 to 0.7 mmol/L (mEq/L), although in the majority of patients this degree of hypokalemia is not usually clinically significant.[16] The elderly patients receiving digitalis or patients with pretreatment ventricular ectopic activity, coronary artery disease, or left ventricular dysfunction may be at high risk, however, for ventricular arrhythmias and sudden death from diuretic-induced hypokalemia.[16] In the Multiple Risk Factor Intervention Trial (MRFIT), patients treated with diuretic therapy for hypertension clearly showed increased mortality.[19]

During short-term therapy, diuretics increase serum cholesterol and triglyceride levels without increasing high-density lipoprotein (HDL) cholesterol, but a consistent alteration in lipids or lipoproteins has not been shown in long-term trials.[16] Diuretics may blunt diet-induced reductions in serum cholesterol, and their use may need to be restricted in the patient with abnormal lipoprotein metabolism.[16] Diuretics also aggravate glucose intolerance and may exacerbate gout in predisposed patients. In the EWPHE trial, an increase in fasting blood glucose and glucose intolerance was observed during diuretic therapy.[11]

There are several theoretical contraindications to the use of diuretics in the elderly. Diuretics decrease total body water and have a tendency to produce hypokalemia, which predisposes the patient to arrhythmias. If diuretic therapy is initiated in low doses (eg, hydrochlorothiazide 25 mg/d), the incidence of adverse effects is low.[7] Should creatinine clearance decline below 0.58 mL/s (35 mL/min), thiazides become ineffective, and loop diuretics may be substituted.

β-Blockers

β-Blockers have been recommended as initial therapy for hypertension in younger patients (<50 years of age), patients with a rapid resting pulse, and those with ischemic heart disease.[2] Since the elderly have decreased β-receptor sensitivity and decreased renin activity, β-blockers are not recommended as first-line therapy for elderly patients.[7] In prospective, controlled trials, the overall response rate for propranolol has been reported to be only 20 to 50 percent in elderly populations.[3,7]

Lethargy, dizziness, fatigue, weakness, nightmares, depression, dyspnea, sexual dysfunction, and cold extremities are common side effects observed during therapy with β-blockers.[6] In the MRC trial, 16 percent of men and 18 percent of women withdrew from therapy with β-blockers because of adverse effects.[18] Lethargy, nausea, dizziness, headache, dyspnea, Raynaud's phenomenon, and impotence were the most common complaints. In a recent comparative trial of captopril, methyldopa, and propranolol, 13 percent of patients withdrew from therapy with propranolol secondary to adverse effects.[20] Fatigue, lethargy, and sexual disorders were the most frequent reasons for drug withdrawal.

β-Blockers can induce clinically important metabolic abnormalities. During chronic therapy, propranolol decreased HDL cholesterol levels.[21] These effects appear to be limited to β-blockers without intrinsic sympathomimetic or α-blocking activity. Glucose intolerance resulting from an increase in serum glucose and a decrease in insulin secretion may occur with nonselective β-blockers; this metabolic effect is most important in patients with insulin-dependent diabetes mellitus.[3] β-Blockers also may mask the symptoms of hypoglycemia, which may present a problem in elderly patients with diabetes mellitus.

Sympatholytics

Clonidine, guanabenz, and methyldopa effectively control blood pressure in 50 to 60 percent of hypertensive patients when used as monotherapy, and the addition of a diuretic increases the response rate in most patients. The relative lack of contraindications, the absence of metabolic abnormalities, and a predictable side effect profile are the major advantages of the sympatholytic agents for the treatment of hypertension.[22] As monotherapy, these agents have not been thoroughly studied in elderly hypertensive patients. In an uncontrolled trial of guanabenz in elderly patients, systolic blood pressure was reduced at least 20 mmHg in 50 percent of patients.[23] In the EWPHE study, the addition of methyldopa to initial diuretic therapy produced a sustained antihypertensive effect, and the combination produced a 40 percent decrease in cardiovascular mortality compared with placebo.[15] Unfortunately, methyldopa was not evaluated as monotherapy.

Despite the absence of contraindications and metabolic alterations associated with the use of sympatholytic drugs for the management of hypertension, these agents are poorly tolerated by many patients. The most common side effects—lethargy, depression, orthostatic hypotension, and impotence—are related to the central nervous system action of the sympatholytics.[22] In the HDFP study, 27 percent of patients discontinued therapy with methyldopa as a result of adverse effects related to treatment.[17] In another study 20 percent of patients withdrew from methyldopa therapy because of side effects including fatigue, lethargy, sexual dysfunction, sleep disorders, head-

ache, and dizziness.[20] Although there is no evidence that the incidence of adverse effects with sympatholytics is higher in elderly patients, the nature of the effects may be particularly disturbing to the patient over 60 years of age.

NONTRADITIONAL THERAPY FOR HYPERTENSION IN THE ELDERLY

Calcium Channel Blockers

Calcium channel blockers reduce blood pressure through a direct effect on arterial smooth muscle tone.[24] Calcium channel blockers provide effective blood pressure control either as monotherapy or combined with other antihypertensive agents such as a diuretic, and the effect is proportional to the magnitude of pretreatment blood pressure. Although diltiazem, nifedipine, and verapamil have similar efficacy in patients with mild to moderate hypertension, the choice of a particular calcium antagonist often depends on the patient's underlying disease state and anticipated side effects. Calcium channel blockers are considered to be effective antihypertensive agents in the elderly and may be considered as alternatives to traditional stepped-care therapy for this population by many clinicians.[7] Their usefulness may be limited by potent vasodilatory actions.

Adverse effects of calcium channel blockers can be predicted from their pharmacological profile.[24,25] Because nifedipine is a potent peripheral vasodilator, headache, flushing, and peripheral edema are more common than with verapamil or diltiazem. Up to 10 percent of patients using nifedipine may experience edema, which occasionally requires the addition of a diuretic. Diltiazem, and especially verapamil, may cause disturbance of atrioventricular conduction; the negative inotropic effects of verapamil may further depress left ventricular contractility in patients with poor ventricular function. Gastrointestinal disturbances, including constipation and nausea, occur most frequently with verapamil.

Calcium channel blockers neither alter lipoprotein metabolism nor impair potassium or uric acid hemeostasis. Calcium channel blockers, especially nifedipine, however, may impair insulin secretion and worsen glucose tolerance during short-term administration in nondiabetic patients.[26] An additive antihypertensive effect has not been observed with the combination of a calcium antagonist and a diuretic.

ACE Inhibitors

Based on few side effects and good quality-of-life profile, ACE inhibitors can be considered as first-line agents for antihypertensive therapy in the elderly. They block the conversion of angiotensin I to angiotensin II, which results in a decrease in aldosterone secretion, lowered peripheral vascular resistance, and a decrease in blood pressure.[27] ACE inhibitors do not interfere with normal autonomic and cardiovascular reflex function; thus, patients do not experience the reflex tachycardia common with other antihypertensive medications (vasodilators) that reduce peripheral resistance. In addition, ACE inhibitors do not depress cardiac function or impair metabolic, central nervous system, or sexual function.[7] Currently three ACE inhibitors, captopril, enalapril, and lisinopril, are approved for the treatment of mild hypertension. Blood pressure is normalized in approximately 50 to 70 percent of patients treated with an ACE inhibitor alone.[28–30]

Despite reduced plasma renin activity in the elderly, captopril is equally effective in elderly hypertensive patients as in younger patients.[7] Corea et al[31] studied 20 hypertensive patients (diastolic blood pressure $\geq$ 95 mmHg) 65 years of age or older. Patients were randomly assigned to receive captopril, 50 mg twice daily, or chlorthalidone, 25 mg once daily, for three months. There was a significant ($P < .01$) decrease in blood pressure in both groups after three months. Metabolic changes observed in the chlorthalidone group were significantly increased in plasma glucose and triglycerides and decreased in serum potassium compared with baseline values. Renal function was unchanged by either therapy.

In a randomized, crossover trial in elderly (>70 years of age) hypertensive patients, captopril was compared with a hydrochlorothiazide-triamterene combination.[32] The two regimens were comparable in efficacy, and only one patient required more than 25 mg of captopril daily to obtain the desired therapeutic response. The diuretic combination caused a significant ($P < .001$) increase in blood urea nitrogen, uric acid, and creatinine values, while captopril produced no adverse biochemical changes.

In a separate study, the efficacy and safety of captopril were evaluated in more than 2,000 hypertension patients, 1,400 of whom were 60 years of age or older.[33] Therapy was initiated with 50 to 150 mg of captopril daily, and a diuretic could be added at the physician's discretion. A significant decrease in arterial pressure was observed as early as day 15, and the response was similar regardless of age. Overall, captopril was well tolerated; the incidence of side effects was less than 2 percent by day 90. There was a trend toward a lower incidence of side effects in the elderly patients.

Virtually all of the side effects reported with captopril have been reported with enalapril and lisinopril. This finding is interesting in that many of the side effects associated with captopril have been attributed to the presence of a sulfhydryl group on the captopril molecule. Yet, this moiety is missing in the molecular structure of ena-

lapril and lisinopril.[34,35] Skin rash, dizziness, and loss of taste are more often reported with captopril, while cough, fatigue, diarrhea, and headache are more common with enalapril and lisinopril.[35]

Symptomatic hypotension may occur with the first dose of ACE inhibitors, especially in patients who are volume depleted from monotherapy with a diuretic. This effect occurs within one to two hours after administration of captopril and resolves rapidly, but may be delayed for six to eight hours after enalapril and last for 24 hours or longer.[36] Decreased renal clearance of enalapril and an increased hypotensive response have been observed in elderly (aged 65 to 78 years) volunteers during chronic administration.[37] There are no long-term trials in elderly hypertensive patients reported to date with lisinopril.

ACE Inhibitors Combined with Diuretics

The combined use of a diuretic and an ACE inhibitor in hypertensive patients produces an additive effect on blood pressure (Figure 1). By blocking the diuretic-induced activation of the renin-angiotensin-aldosterone system, the ACE inhibitor prevents attenuation of the antihypertensive effects of the diuretic.[27] Response rates greater than 85 percent have been achieved with a captopril-diuretic combination in patients with mild to moderate hypertension.[28–30] Similarly, enalapril plus hydrochlorothiazide normalized blood pressure in over 85 percent of patients with mild to moderate hypertension, compared with 67 percent with enalapril alone.[38] Lisinopril plus hydrochlorothiazide has demonstrated a response rate similar to enalapril and captopril combined with hydrochlorothiazide.[34]

An additive effect has been observed with the captopril-diuretic combination in elderly hypertensive patients. In a randomized, double-blind trial, the efficacy of captopril (25 to 50 mg/d) plus hydrochlorothiazide (25 mg/d) was compared with placebo in 56 hypertensive patients over the age of 65 years.[39] Blood pressure was normalized in 97 percent of patients in the treatment group at 12 weeks, compared with only 8 percent of patients in the placebo group.

In a recent study, the response to twice daily dosing of 25 mg of captopril was evaluated in 99 hypertensive patients over 60 years of age.[40] If the diastolic blood pressure was 90 mmHg or higher after two weeks, patients were randomly assigned to receive 50 mg of captopril twice daily or 25 mg of captopril plus 15 mg of hydrochlorothiazide twice daily. Captopril alone produced a response in 51 percent of patients; overall, 76 percent of patients responded. There was a greater response with combination therapy (−12 mmHg) than with captopril alone (−5 mmHg).

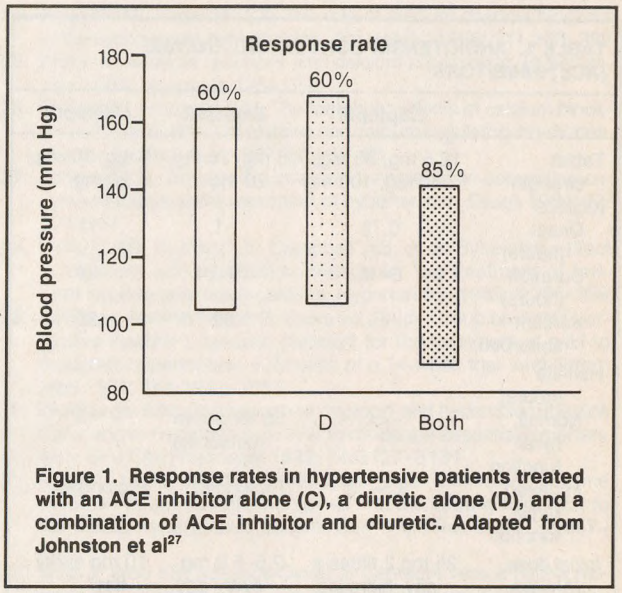

Figure 1. Response rates in hypertensive patients treated with an ACE inhibitor alone (C), a diuretic alone (D), and a combination of ACE inhibitor and diuretic. Adapted from Johnston et al[27]

Captopril given at doses of 50 to 100 mg/d normalized blood pressure in seven of 15 hypertensive patients aged 67 to 87 years, and hypertension was controlled in an additional five patients when a diuretic was added.[41] Renal blood flow and the glomerular filtration rate were unchanged during treatment.

In a postmarketing surveillance study, hypertensive patients aged 65 years or over were treated with captopril with or without the addition of a diuretic.[42] Four hundred eighteen patients received treatment for at least 12 months; mean values for systolic and diastolic blood pressure were significantly ($P < .001$) reduced compared with baseline values. More important, renal function was unchanged during therapy in patients with both normal and impaired renal function at baseline.

The ACE inhibitors reduce preload and afterload, thus making them potentially useful agents in patients with congestive heart failure. ACE inhibitors also blunt the effect of diuretic-induced potassium loss, although they may increase the risk of hyperkalemia. Hyperkalemia can be avoided with cautious use of potassium-sparing diuretics and potassium supplements with judicious use of serum potassium monitoring (Table 1 displays general information in the use of ACE inhibitors).

EFFECTS OF THERAPY ON QUALITY OF LIFE

Three major components contribute to the quality-of-life assessment: functional capacity, patients' perceptions, and

TABLE 1. ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

	Captopril	Enalapril	Lisinopril
Tablet strength	12.5 mg, 25 mg, 50 mg, 100 mg	5 mg, 10 mg, 20 mg	5 mg, 10 mg, 20 mg
Kinetics			
Onset (hours)	0.75	1	1
Duration (hours)	6–12	18–24	24
Percent absorbed	75	60	25
Half-life (hours)			
Normal renal function	<2	35 for active metabolite	12
Impaired renal function	3.5–32	Prolonged	Prolonged
Initial dose (Always calculate creatinine clearance to initiate dosing)	25 mg 2 times a day. Increase 25 mg per dose at 1- to 2-wk intervals (may start with 12.5-mg dose in elderly)	2.5–5.0 mg every day. Increase 2.5–5.0 mg at 1- to 2-wk intervals; some need dosing twice daily	10 mg every day. Increase 5–10 mg at 1- to 2-wk intervals
Current maximum dose	≤150 mg	40 mg	40 mg

Monitoring: *Orthostatic blood pressure, sitting blood pressure, urinalysis for proteinuria; observe for chest pain, hypotension, headache, dizziness, fatigue, abdominal pain, dysgeusia, dyspnea, cough, pruritis, rash.*
Patient Information: *Take captopril on empty stomach; do not stop therapy. Contact physician if any of the above symptoms occur. Do not use salt substitutes without consulting physician first.*

their reported symptoms.[43] Poor compliance with treatment is one of the major responses of patients who experience an impaired quality of life; therefore, for antihypertensive therapy to be truly successful, blood pressure control should be achieved without a loss in quality of life. Available data suggest that an acceptable quality of life is not found with most antihypertensive drugs. In a recent survey of perceptions of the effect of therapy on quality of life, only 48 percent of patients felt an improvement was achieved during therapy.[44] Relatives perceived that fewer than 1 percent (1 of 75) of patients had experienced any improvement.

A large double-blind, randomized trial assessed the effects of antihypertensive therapy with captopril, methyldopa, or propranolol on quality of life. Measures included (1) sense of well-being and satisfaction with life, (2) physical state, (3) emotional state, (4) intellective function, and (5) ability to perform in social roles.[20] After 24 weeks of therapy, all three groups attained a similar degree of blood pressure control. Patients taking captopril reported an increased sense of well-being as compared with the other treatment groups. In addition, only 8 percent of patients treated with captopril compared with 13 and 20 percent of patients taking propranolol or methyldopa, respectively, withdrew from the study as a result of adverse effects. Patients taking captopril scored significantly higher on measures of general well-being and physical symptoms than did patients taking methyldopa or propranolol. The results of this study emphasize the influence of drug selection on the patients' quality of life. These findings are of clinical significance when one considers the potential impact of subjective side effects on patient compliance with drug therapy for what is generally considered to be a symptomless disease.

CONCLUSIONS

Results from the Framingham study and several prospective, controlled trials in the elderly population document the benefits of antihypertensive therapy. Effective treatment reduces cerebrovascular and cardiovascular morbidity and mortality. An undesirable component of therapy, however, is the risk of complications associated with antihypertensive treatment.

In the stepped-care approach, therapy is initiated with either a diuretic or a β-blocker (or other sympatholytic agent in the elderly). In controlled trials, this approach to therapy has been associated with a high frequency of side effects, a reduced quality of life, and a high rate of withdrawal or noncompliance with therapy. An alternative approach to antihypertension management in the elderly patient is the use of an ACE inhibitor or a combination of an ACE inhibitor plus a diuretic. Combination therapy uses a lower dose of each agent, which results in a lower incidence of side effects. Diuretic-induced metabolic alterations, especially hypokalemia, are blunted by the addition of the ACE inhibitor; this benefit is not observed with other antihypertension drug combinations, including a diuretic plus a calcium antagonist. Most important, treatment with an ACE inhibitor-diuretic combination preserves the quality of life that is so important to the elderly patient.

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