Abundant evidence has accumulated showing that angiotensin converting enzyme (ACE) inhibitors reduce long-term cardiovascular morbidity and mortality rates in patients with heart failure and myocardial infarction. Fewer completed trials have assessed their potential benefits in this regard in hypertensive subjects, but evidence of benefit is beginning to accrue from studies examining patients with hypertension, particularly in the presence of diabetes and after infarction.

Ongoing trials of blood pressure (BP) lowering using ACE inhibition fall into three main categories: 1) those comparing ACE inhibitors with older drugs such as diuretics and β blockers; 2) those examining more aggressive versus less aggressive lowering of BP; and 3) those investigating BP lowering in patients at high risk for a cardiac event. Among those in the last group is the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), which examines the effects of perindopril-based ACE inhibitor therapy in both normotensive and hypertensive patients who have survived a stroke. This trial is particularly important because it serves as a model for studies of BP lowering across a wide range of BP and BP-related conditions. Am J Hypertens 2001;14:270S–275S © 2001 American Journal of Hypertension, Ltd.

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Evidence for the benefits of angiotensin-converting enzyme (ACE) inhibitors in reducing cardiovascular (CV) morbidity and mortality in patients with myocardial infarction (MI) and congestive heart failure is well established. Few trials have been completed in patients with hypertension to determine whether ACE inhibitors can provide similar protection. Hypertensive patients carry a high risk of CV complications, particularly stroke. In fact, there is a strong association between the level of blood pressure (BP) and the risk of stroke. This association is steep and continuous, with no lower level identified below which the risk of stroke does not continue to decline (Fig. 1). This is particularly significant because stroke is a leading cause of death worldwide, even in developing countries. Furthermore, as the population ages, it will become an even more prominent mortality risk and, by 2020, will be the fourth leading cause of death worldwide.

Several recent trials have sought to address the role of ACE-inhibitor therapy in decreasing the risk of stroke morbidity and mortality. This review will discuss trials that have examined the benefits of ACE inhibitors versus other agents in high-risk patients, including those with hypertension and diabetes, and the benefits of more aggressive versus less aggressive lowering of BP in high-risk patients. One ongoing trial, the Perindopril Protection against Recurrent Stroke Study (PROGRESS), will be discussed in detail because it may serve as a model for studies of BP lowering therapy in patients with a broad range of BP.

Completed Trials

United Kingdom Prospective Diabetes Study (UKPDS)

Type 2 diabetes and hypertension commonly coexist, and each of these conditions impart an increased risk of CV complications. Their combined presence adds an even greater risk. The UKPDS group sought to determine whether “tight” BP control (goal < 150/85 mm Hg), using either the ACE inhibitor captopril or the β blocker atenolol, diminishes the risk of complications in diabetic patients compared with patients maintaining “less tight” BP control (goal < 180/105 mm Hg).

This multicenter randomized, controlled trial, which was embedded in a larger trial of tight versus less tight glucose control, included 1148 hypertensive patients with which is supported by funds from Servier.

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Type 2 diabetes (mean age 56 years, mean BP at entry 160/94 mm Hg): 758 patients were randomly assigned to tight BP control and 390 to less tight control. Median follow-up was 8.4 years. Clinical end points were fatal and nonfatal events related to diabetes and all-cause mortality. Surrogate measures of microvascular disease included urinary albumin excretion and retinal photography.

Mean BP during follow-up was reduced significantly more in the group assigned to tight BP control (144/82 mm Hg) than in the group assigned to less tight control (154/87 mm Hg) ($P < .0001$). Tight control yielded a 24% reduction in diabetes-related end points, a 32% reduction in diabetes-related deaths, a 44% reduction in strokes, and a 37% reduction in microvascular end points. The ACE inhibitor and the $\beta$ blocker were about equally effective in preventing diabetes-related end points and diabetes-related deaths, particularly strokes.

In summary, tight BP control was shown to be extremely beneficial in the prevention of macrovascular disease—to an even greater extent than tight glucose control, which was shown to yield a benefit in microvascular disease but only a nonsignificant benefit in macrovascular disease.

**Swedish Trial in Old Patients With Hypertension-2 (STOP-2) Study**

The STOP-2 study$^2$ compared treatment with “conventional” antihypertensive agents ($\beta$ blockers and diuretics) versus that with two newer (but well established) antihypertensive classes of agents, the calcium channel blockers and ACE inhibitors. The prospective randomized trial included 6614 patients, aged 70 to 84 years, with hypertension (systolic BP $\geq$ 180 mm Hg or diastolic BP $\geq$ 105 mm Hg, or both). End points were fatal stroke, fatal MI, and other fatal CV disease (CVD) events.

Blood pressure decreased to similar levels in all treatment groups. Specifically, the combined primary end points occurred in 221 of 2213 patients in the patients receiving the conventional agents and 438 of 4401 patients in the ACE inhibitor/calcium channel blocker group, yielding a relative risk (RR) of 0.99 (95% confidence interval [CI] 0.84 to 1.16, $P = .89$).

This study presented the first evidence that standard hypertensive agents can yield a benefit in elderly subjects similar to that of newer agents. Angiotensin converting enzyme inhibitors produced results similar to those of calcium channel blockers in terms of BP reduction, but ACE inhibitors tended to yield a slightly greater benefit in terms of prevention of MI and stroke, suggesting that ACE inhibitors may have benefits beyond BP lowering.

**Heart Outcomes Prevention Study (HOPE)**

Angiotensin-converting enzyme inhibitors are known to improve CV outcomes among patients with left ventricular
(LV) dysfunction, with or without heart failure. The HOPE study\textsuperscript{6} investigated the benefits of the ACE inhibitor ramipril in 9297 patients at high risk of CV events but without either LV dysfunction or heart failure. “High risk” meant that these patients had evidence of vascular disease or diabetes plus one other CV risk factor. They did not, however, have a low ejection fraction or heart failure.

In this controlled trial, patients were randomly assigned to ramipril 10 mg/day or matching placebo for a mean of 5 years. The primary end point was a composite of MI, stroke, and death from CV causes.

The reductions in systolic BP were relatively modest with ramipril, at only about 3 mm Hg. However, the benefits in terms of the primary end points were remarkable and significant. A total of 651 patients receiving ramipril (14%) had a primary end point, compared with 826 patients (17.8%) receiving placebo (RR 0.74, 95% CI 0.70–0.86). Ramipril treatment reduced rates of death from CV causes (6.1% v 8.1% with placebo, RR 0.74, \( P < .001 \)), MI (9.9% v 12.3%, RR 0.80, \( P < .001 \)), stroke (3.4% v 4.9%, RR 0.85, \( P = .002 \)), cardiac arrest (0.08% v 1.3%, RR 0.63, \( P = .03 \)), heart failure (9.0% v 11.5%, RR 0.77, \( P < .001 \)), and complications related to diabetes (6.4% v 7.6%, RR 0.84, \( P = .03 \)).

The investigators concluded that the 3-mm Hg reduction in BP was not by itself sufficient to account for the beneficial effects of ACE inhibition. The other factors that contribute to the reductions in morbidity and mortality are not yet determined.

Some Ongoing Trials

World Health Organization–International Society of Hypertension (WHO–ISH) Blood Pressure Lowering Treatment Trialists’ Collaboration

The WHO-ISH collaborative study\textsuperscript{7} is a prospectively planned overview of ongoing randomized trials of antihypertensive agents. This meta-analysis should provide important information about the relative benefits of the newer antihypertensive agents, such as ACE inhibitors and calcium channel blockers, compared with older agents on major causes of CV mortality and morbidity. It is also examining the relative benefits of more versus less aggressive BP control.

A total of 37 trials have qualified for this collaboration, and 36 have agreed to collaborate. This will yield a database of 271,000 patients and \( > 1 \) million patient-years. The collaborators from the various trials have agreed to make their individual patient data available for a pooled analysis by subgroups that are relatively homogeneous. Primary outcomes are stroke, MI, total cardiac events, and total CV mortality. Initial results with about 100,000 patients will be presented shortly. Within the next couple of years, data from \( > 250,000 \) patients should be available for analysis.

The collaboration will analyze data from a number of major trials involving ACE inhibitors. These are best grouped into three sets: 1) one set of trials in patients with hypertension, 2) a second set in patients with diabetes and/or renal disease, and 3) a third set in high-risk patients with preexisting CVD.

The first group of studies, in hypertensive patients, includes the Hypertension in the Very Elderly Trial (HYVET), the Australian National Blood Pressure Study 2 (ANBP2), the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT), and the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT). The second group, in patients with diabetes and/or renal disease, comprises the study of diabetic patients with hypertension (DIAB-HYCAR), the African American Study, the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, and the Bergamo Nephrologic Diabetes Complication Trial (BENEDICT). The third group, in patients with preexisting CVD, is composed of PROGRESS, the European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA), and the Perindopril Protection Against Recurrent Stroke Study (PEACE).

Ongoing Trials in Patients With Hypertension

Hypertension in the Very Elderly Trial (HYVET)

The HYVET study\textsuperscript{8} is a multicenter, open, randomized, controlled trial that is investigating the effect of antihypertensive treatment (perindopril plus indapamide) on the incidence of stroke in patients aged \( > 80 \) years (Table 1). Secondary end points include total CV mortality and morbidity.

Australian National Blood Pressure Study 2 (ANBP2)

The intention of ANBP2 is to compare the difference in total CV events occurring with ACE inhibitor–based treatment versus diuretic-based BP treatment in patients 65 to 85 years of age with hypertension.\textsuperscript{9} It is being conducted in some 6000 patients attending general practices throughout Australia and should be completed by 2002. It is a randomized, controlled study using open labeling of study treatments with blinded assessment of end points.

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

Only \( \beta \) blockers and diuretics have been shown to reduce long-term morbidity and mortality in hypertensive patients. The ALLHAT trial,\textsuperscript{10} sponsored by the National Heart, Lung, and Blood Institute, is comparing the effects of chlorthalidone, a diuretic, and three types of antihy-
tensive agents—doxazosin (α-antagonist), amlodipine (calcium channel blocker), and lisinopril (ACE inhibitor)—on the incidence of CVD in patients with hypertension. The doxazosin portion of this study has been terminated prematurely due to a significantly higher incidence of congestive heart failure events in the doxazosin group compared with the chlorthalidone group. A beneficial effect of doxazosin at the scheduled trial termination was considered highly unlikely. There were also negative trends for stroke and for combined coronary heart disease (CHD), particularly coronary revascularizations and angina.

Anglo-Scandinavian Cardiac Outcome Trial (ASCOT)

Anglo-Scandinavian Cardiac Outcome Trial aims to recruit 18,000 patients with hypertension and other risk factors for CVD. It will address two main issues: 1) whether a traditional drug regimen for treating hypertension (ie, a β blocker with or without a diuretic) is better able to prevent MI than a regimen including a calcium channel blocker (with or without an ACE inhibitor); and 2) whether the lipid-modifying agent atorvastatin confers a benefit in persons with cholesterol levels in the normal range.

Ongoing Trials in Patients with Diabetes or Renal Disease

DIAB-HYCAR Study

The French DIAB-HYCAR study is comparing the effects of a very low dose of ramipril (1.25 mg, a dose so low that it has little effect on BP) with those of placebo on CV morbidity and mortality in normotensive or hypertensive patients with Type 2 diabetes and persistent albuminuria. A total of 4000 patients are included in this trial.

African American Study

Another study is examining the effect of calcium channel blockade (sustained-release verapamil) or β blockade (atenolol) on progression of diabetic nephropathy in African Americans. A diuretic is being used as second-line therapy if needed to attain the goal BP of < 140/90 mm Hg.

Appropriate Blood Pressure Control in Diabetes (ABCD)

The ABCD trial examined the effect of BP control using nisoldipine or enalapril on diabetic microvascular complications in patients with hypertension and Type 2 diabetes. A total of 470 patients were randomly assigned to tight BP control (diastolic BP < 75 mm Hg) versus moderate BP control with either nisoldipine, a long-acting calcium antagonist, or enalapril. After 1 year of treatment, creatinine clearance stabilized in both the intensive and moderate BP control groups in patients with baseline normoalbuminuria or microalbuminuria. Patients who initially had overt albuminuria showed a steady decline in creatinine clearance of 5 to 6 mL/min × 1.73 m² throughout the follow-up period, whether receiving intensive or moderate therapy. There was also no difference between the agents with regard to progression of albuminuria. However, intensive therapy yielded a lower overall incidence of deaths, 5.5% vs 10.7% (P < .037). Over the 5-year follow-up, there was no difference with regard to progression of diabetic retinopathy and neuropathy. Furthermore, no difference in effects on diabetic retinopathy or neuropathy was seen between enalapril and nisoldipine.

Bergamo Nephrologic Diabetes Complication Trial (BENEDICT)

The BENEDICT study is examining whether ACE inhibitors and calcium antagonists in combination have
renoprotective properties beyond those of either agent alone. The study is including 2400 patients with Type 2 diabetes and hypertension with normal albumin excretion. In the first part of the study, patients are being randomly assigned to treatment for 3 years with slow-release verapamil, the ACE inhibitor trandolapril, or a combination of the drugs, and placebo. In the second part of the study, progression to macroalbuminuria will be evaluated in patients in whom microalbuminuria developed during the first phase. These patients are being randomly assigned to 2 years of treatment with trandolapril alone or combined with verapamil.

Ongoing Trials in Patients With Preexisting CV Disease

European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPA)

Another group of ongoing clinical trials is evaluating the effects of antihypertensive therapy in patients with established CVD. These studies include EUROPA, a European trial examining the effect on rate of cardiac events with perindopril in patients with stable CHD but no clinical heart failure. This double-blind, placebo-controlled, multicenter study will last 3.5 years.

Prevention of Events With Angiotensin-Converting Enzyme Inhibition (PEACE)

An earlier study in hypertensive patients with LV hypertrophy showed that a β blocker and a calcium channel blocker were equally effective as antihypertensive agents, but that they showed different effects on LV mass. After 6 months, only those patients receiving verapamil showed reductions in LV mass as determined echocardiographically. The PEACE trial is addressing whether therapy with an ACE inhibitor produces additional benefit beyond that of BP control. It will determine if therapy with trandolapril yields a reduction in the incidence of CV death, nonfatal MI, or revascularization procedures. Investigators have randomly assigned 8100 patients who have coronary disease, but a preserved ejection fraction, to trandolapril or placebo.

Perindopril Protection Against Recurrent Stroke Study (PROGRESS)

The PROGRESS trial is examining the effects of perindopril for secondary prevention of stroke and transient ischemic attacks. The rationale for this randomized, placebo-controlled study is based on evidence from both observational studies of the association between BP levels and stroke risk and randomized, controlled trials of BP-lowering regimens. The aim of PROGRESS is to provide reliable evidence about the balance of benefits and risks conferred by ACE inhibitor–based BP lowering in patients with cerebrovascular disease.

Therapy with an ACE inhibitor was chosen because ACE inhibitors are well tolerated, safe, and effective. They do not produce postural hypotension, which is particularly important in patients who have had a stroke. Perindopril was chosen because it is long acting, can be given once daily, and does not have a first-dose effect (ie, a dramatic decrease in BP initially). Most important, perindopril does not decrease cerebral blood flow, a particularly relevant consideration in patients with cerebrovascular disease.

Perindopril Protection Against Recurrent Stroke Study is being conducted in 172 collaborating centers around the world: Australia, New Zealand, China, France, Belgium, Italy, Japan, Sweden, the United Kingdom, and Ireland. It includes 6105 participants with a history of stroke or transient ischemic attack; 60% of these patients have hypertension and 40% are normotensive. (Note that, as stated earlier, the risk of stroke decreases when BP is lowered, regardless of the initial level.) Patients were randomly assigned to perindopril 4 mg, with or without indapamide 2.5 mg, or matching placebo. The primary end point is stroke; secondary end points include other CV events such as MI, CV death, and cognitive decline or dementia. Dementia is considered an important outcome, and there is suggestive data, albeit very limited, that antihypertensive therapy (in this case, with nitrendipine) may reduce the rate of dementia.

Mean follow up in PROGRESS is 41 months; as of March 24, 2000, a total of 20,059 patient-years had accumulated; by February 2001, the total will reach 25,200 patient-years. The first patients now have 58 months of follow up. As of March 24, 2000, a total of 603 strokes (fatal or nonfatal) had occurred, representing a rate of 3.2%; in all, 226 patients have had an MI (1.1%), for a total CV event rate of approximately 4%. These numbers should ensure that the study has more than sufficient power to achieve its primary objective, which is to provide reliable evidence regarding the balance of benefits and risks conferred by an ACE inhibitor–based BP lowering regimen in patients with cerebrovascular disease.

Conclusions

Ongoing studies with ACE inhibitors should yield an abundance of information about the role of this class of agents in hypertension. Already known to be effective BP-lowering agents, ACE inhibitors may have other beneficial effects. These studies will show the impact of ACE-inhibition therapy on rates of CVD, and in particular stroke, compared with that of other newer drugs (eg, calcium antagonists) and older drugs (eg, β blockers). They will also provide insight into their efficacy in a range of patients, including those with established CVD and the elderly. In addition, valuable insight will be gained as to the effects of ACE inhibition on the course of renal disease in patients with diabetes and in those with hypertension.
This knowledge will better arm clinicians to treat what is a leading cause of death and disability worldwide.

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