

The Anti-Ischemic Potential of Angiotensin-Converting Enzyme Inhibition: Insights from the Heart Outcomes Prevention Evaluation Trial

BERTRAM PITT, M.D.

Cardiology Division, University of Michigan Medical Center, Ann Arbor, Michigan, USA

Summary: Therapy with an angiotensin-converting enzyme (ACE) inhibitor is established for reducing excessive blood pressure, reducing mortality in patients with congestive heart failure (CHF), preventing the development of CHF in patients with asymptomatic left ventricular (LV) dysfunction, and preventing death and CHF when initiated early after the onset of acute myocardial infarction (MI). Although these benefits have been attributed largely to hemodynamic mechanisms, recent preclinical and clinical evidence reveal ACE inhibition as potent in preventing ischemic events and in blocking an array of ischemic processes, including atherogenesis. A major contributor to this new evidence is the large, placebo-controlled Heart Outcomes Prevention Evaluation (HOPE) trial, which found that the ACE inhibitor ramipril (10 mg daily) prevented MI and other ischemic events in patients with a broad range of cardiovascular (CV) risks (including coronary artery disease, stroke, peripheral vascular disease, or diabetes plus one additional risk factor) but no LV dysfunction or history of heart failure at baseline. The data from the HOPE trial suggest a greatly expanded role for ramipril in the prevention and management of CV disease.

Key words: angiotensin-converting enzyme inhibitors, ischemia, congestive heart failure, left ventricular dysfunction, ramipril, diabetes, stroke

Introduction

Chronic therapy with angiotensin converting enzyme (ACE) inhibitors has been proven to effectively lower excessive blood pressure, reduce hospitalization and mortality in patients with congestive heart failure (CHF), and prevent the development of

CHF in patients with asymptomatic left ventricular (LV) systolic dysfunction. In addition, routine early and short-term use of ACE inhibitors in acute myocardial infarction (MI) has been convincingly shown to prevent death and the development of CHF.¹ Initially, the benefits of ACE inhibition were attributed primarily to hemodynamic activity that was modestly anti-ischemic at best. However, recent preclinical and clinical studies have indicated that ACE inhibitors are potent in preventing MI and other ischemic events and in blocking the causes of these events, such as atherogenesis and coronary vasoconstriction.^{2,3} In the most compelling of the clinical studies, the placebo-controlled Heart Outcomes Prevention Evaluation (HOPE) trial, the ACE inhibitor ramipril (10 mg daily) was significantly associated with the prevention of definite or possible ischemic events (including MI, coronary revascularization, cardiovascular death, and stroke) in patients with baseline cardiovascular (CV) disease or diabetes mellitus plus one additional risk factor but no LV dysfunction.³ Thus, the contribution of anti-ischemic activity to the long-established benefits of ACE inhibition is probably greater than previously recognized, and it is likely that ACE inhibition with ramipril will play an important role in the prevention of CV events.

Established Settings for Angiotensin-Converting Enzyme Inhibition

Left Ventricular Dysfunction

ACE inhibitors are widely endorsed as routine therapy for patients with CHF. In the placebo-controlled Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), the addition of the ACE inhibitor enalapril to standard therapy (including other vasodilators) in patients with severe heart failure significantly reduced mortality compared with placebo. In the second Veteran's Administration Cooperative Vasodilator-Heart Failure Trial (V-HeFT II), patients receiving digoxin and a diuretic for chronic CHF had modestly superior survival if they received enalapril rather than isosorbide dinitrate and hydralazine, a vasodilator combination previously found to improve survival; tolerance of enalapril was superior.⁴ In the treatment phase of the placebo-controlled Studies of Left Ventricular Dysfunction (SOLVD) trial, patients with CHF that was preponderantly mild or moderate had a 16% reduction in mortality when enalapril was added to standard medication (diuretics and digoxin) for CHF.¹ These results are

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Address for reprints:

Bertram Pitt, M.D.
Cardiology Division
University of Michigan Medical Center
1500 E. Medical Center Drive
Ann Arbor, MI 48109-0366, USA

consistent with the findings of a meta-analysis of randomized trials of CHF treatment with various ACE inhibitors, including captopril, enalapril, and ramipril. This analysis showed that most of the survival benefit was due to prevention of the progressive deterioration of LV function, with prevention of arrhythmic events a possible additional contributor. Both effects are largely attributed to prevention of ventricular remodeling as well as to the inhibition of myocardial fibrosis.

Two trials were critical in validating ACE inhibition for patients with asymptomatic LV dysfunction. In the prevention phase of the SOLVD trial, enalapril was associated with a non-significant trend toward reduced mortality; however, during the 4-year period of follow-up, enalapril treatment resulted in significant reduction in the incidences of newly diagnosed CHF and hospitalization for CHF.¹ In the Survival and Ventricular Enlargement (SAVE) trial, the initiation of long-term treatment with captopril shortly after acute MI in patients with LV dysfunction was significantly associated with a reduced risk of death, new CHF, and hospitalization for CHF.¹

Acute Myocardial Infarction

The early initiation of chronic ACE inhibition after acute MI is validated for patients with heart failure and/or LV dysfunction. In the Acute Infarction Ramipril Efficacy (AIRE) study, oral ramipril therapy that began 3 to 10 days after acute MI complicated by CHF regardless of LV ejection fraction was associated with a significant reduction in mortality at a mean follow-up of 15 months;⁵ a related study found that the magnitude of this mortality had increased 3 years after the closure of the AIRE study.¹ Similar therapy withtrandolapril for patients with reduced LV function in the Trandolapril Cardiac Evaluation (TRACE) study was associated with reductions in overall mortality, CV mortality, and progression to severe heart failure after follow-up of 24 to 50 months.⁶

Large placebo-controlled trials have also explored the initiation of ACE inhibition within the first 10 days after the onset of symptoms of acute MI in unselected patients. In the CONSENSUS II trial, the initiation of a 6-month course of enalapril (intravenous and subsequent oral therapy) within 24 h of symptom onset had no beneficial effect on mortality in unselected patients or high-risk subgroups, including patients with CHF.¹ However, in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)-3 study, the Fourth International Study of Infarct Survival (ISIS-4), and the Survival of Myocardial Infarction Long-term Evaluation (SMILE) trial, the oral administration of an ACE inhibitor (lisinopril, captopril, and zofendopril, respectively) to within 24 h after onset of symptoms led to a greater chance of survival during the acute phase after 5–6 weeks of such therapy. An analysis of these and other pertinent trials indicates that the short-term mortality benefit is largely confined to patients with anterior MI.¹

Hypertension

In patients with hypertension, ACE inhibitors have been judged as effective as beta blockers and thiazide diuretics in re-

ducing blood pressure and slightly less effective than calcium antagonists. There is substantial, but not conclusive, evidence that ACE inhibitors are more effective than any other standard antihypertensive drug class in reversing hypertensive LV hypertrophy,⁴ a forecaster of CHF, MI, and other CV events.⁷ Whether such reversal prevents CV events is uncertain.⁴

The ACE inhibitors have been shown to have beneficial effects in hypertensive patients with coexistent diabetes, partly because they reduce proteinuria and slow the progression of diabetic nephropathy in patients with type 1 diabetes and appear to act similarly in type 2 diabetes.¹ Randomized clinical comparisons of an ACE inhibitor and a calcium-channel blocker in both the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET) and Appropriate Blood Pressure Control in Diabetes (ABCD) trial (enalapril vs. nisoldipine) credited ACE inhibition for significant relative reductions in CV events of definite or probable ischemic origin in patients with hypertension and type 2 diabetes. Since ACE inhibition was either similar to (ABCD) or less effective (FACET) than calcium blockade in reducing blood pressure, its superior CV protection has been speculatively attributed to more direct anti-ischemic effects.¹ Further prospective comparison of ACE inhibition to calcium-channel blocking agents and the combination of ACE inhibitor and a calcium-channel blocking agent will, however, be required before any final conclusions as to the relative effectiveness of these agents can be determined.

Anti-Ischemic Effects of Angiotensin-Converting Enzyme Inhibitors: Background to the HOPE Trial

Although the SAVE trial and both phases of the SOLVD trial were conducted primarily to see whether ACE inhibition could prevent the development or progression of CHF and reduce overall CV mortality, they showed that it also reduced the incidence of ischemic CV events, including recurrent MI, and hospitalization for angina pectoris. These benefits emerged roughly 1 year after the initiation of treatment, suggesting that they were due not to the hemodynamic effects of ACE inhibition but to structural effects, such as prevention of the progression of coronary artery disease (CAD) and stabilization of atherosclerotic plaques.¹ Explanations for these benefits are suggested by several lines of evidence:

1. Activation of the renin-angiotensin system (RAS) appears to be an independent predictor of ischemic events. A 1991 clinical report by Alderman *et al.* showed that a high renin profile (determined by plotting plasma renin activity against the urinary excretion of sodium) prior to the initiation of a modified stepped-care drug treatment for mild to moderate hypertension predicted MI during a follow-up of 8.3 years and did so independently of race, gender, and such baseline factors as age, blood pressure, serum cholesterol level, blood glucose level, smoking status, and the presence or absence of diabetes or CV disease.⁸

2. ACE inhibition is a theoretical candidate for anti-ischemic therapy because it reduces the levels of angiotensin II in

the circulation and in vascular tissues. Angiotensin II is both a vasoconstrictor and a promoter of the growth and migration of vascular smooth muscle cells and other processes that contribute to pro-ischemic vascular remodeling.⁹ Angiotensin II causes an increase in smooth muscle cell enzymes such as NADH/NADPH, free radical production, and the LOX-1 receptor responsible for low-density lipoprotein (LDL) cholesterol oxidation as well as the stimulation of various adhesion molecules, growth factors, and cytokines, all while contributing to other sclerotic processes.

3. Preclinical studies have shown that ACE inhibition can counteract the pathologic vasoconstriction of atherosclerotic coronary arteries.² For instance, Finta *et al.* found that the administration of ramipril to rabbits prevented endothelial dysfunction in arteries from rabbits fed an atherogenic diet.¹⁰ Such findings, in turn, are consistent with experimental evidence that ACE inhibition increases the release of nitric oxide and other promoters of vasodilation, possibly by increasing local levels of bradykinin² as well as by inhibiting angiotensin II.

4. In preclinical studies, ACE inhibition was found to oppose several atherogenic processes, including thrombosis, oxidation, proliferation of vascular smooth muscle cells, and local accumulation of neutrophils.²

5. Activation of the RAS may be prothrombotic, since it has been experimentally found to increase plasma levels of plasminogen activator 1 (PAI-1), an inhibitor of endogenous fibrinolysis; moreover, there is preliminary evidence that ACE inhibitors improve endogenous fibrinolytic function in patients with CAD.²

The HOPE Study

The multicenter international HOPE trial explored whether ACE inhibition with ramipril at 10 mg/day or antioxidant therapy with vitamin E could prevent CV events or stroke in at-risk patients without known LV dysfunction.³ Vitamin E therapy was studied because it has been associated with a reduced risk for CV events and stroke in preliminary clinical studies, and oxidation of lipids has been experimentally found to contribute to atherosclerosis.¹¹ This review confines its discussion of the HOPE results to those with ramipril 10 mg/day (a few patients received ramipril at 2.5 mg/day).³

The trial was conducted at 267 centers in 19 countries, including 129 in Canada and 27 in the U.S. Enrollment was limited to patients who were ≥ 55 years old and had currently stable CAD (e.g., not characterized by an episode of acute MI or unstable angina within the past month), peripheral vascular disease, a history of stroke (occurring > 1 month prior to enrollment), or diabetes (type 1 or 2), with at least one additional CV risk factor (hypertension, dyslipidemia, current smoking habit, or microalbuminuria). Exclusion criteria included current use of an ACE inhibitor or vitamin E, CHF, a low ejection fraction (< 0.40), uncontrolled hypertension, or overt nephropathy. The primary endpoint was a composite of MI, stroke, and CV death.^{3,11}

As reported, 9,297 patients were randomized to receive ramipril ($n = 653$) 10 mg/day or placebo ($n = 824$). In the over-

all group, 27% were women, 55% were at least 65 years of age, 88% had CV disease, 47% had hypertension, and 38% had diabetes. An ejection fraction < 0.40 was documented in only 2.6% of 496 patients in an echocardiographic substudy and in 8.2% of 5,183 patients whose records furnished prerandomization measurements of LV function. The ramipril and placebo groups were similar in baseline characteristics.³

The study had been scheduled to accumulate a mean follow-up of 5 years but was terminated between the fourth and fifth year of follow-up because the beneficial effect of ramipril on the primary endpoint was highly significant. This endpoint had been reached by 14.1% in the ramipril group and 17.7% in the placebo group, a significant difference ($p < 0.001$) that yielded a relative risk for ramipril of 0.78 (Fig. 1).³ When each component of the primary endpoint was analyzed separately, ramipril was associated with significantly lower relative risks of 0.75 for overall CV death, 0.80 for MI, and 0.69 for stroke (all $p < 0.001$). The relative risk of death from any cause with ramipril was 0.84 ($p = 0.006$).³

In an analysis of secondary end points, ramipril was significantly associated with lower incidences of revascularization (relative risk, 0.84; $p < 0.001$), cardiac arrest (relative risk, 0.63; $p = 0.03$), development of heart failure (relative risk, 0.77; $p < 0.001$), new diagnosis of diabetes (relative risk, 0.68; $p = 0.002$), and development of diabetic complications (relative risk, 0.84; $p = 0.03$). It was also associated with a statistical trend of fewer hospitalizations for CHF. Ramipril had no effect on the likelihood of hospitalization for unstable angina (Table I).³

Ramipril had a significant favorable effect on the primary end point in men and women and in subgroups defined by the presence or absence of the following baseline characteristics: an age of least 65 years, diabetes, hypertension, microalbuminuria, evidence of CV disease, evidence of CAD, and a history of MI (Fig. 2).³ Among patients with a documented baseline ejection fraction of at least 0.40, the relative risk of reaching the

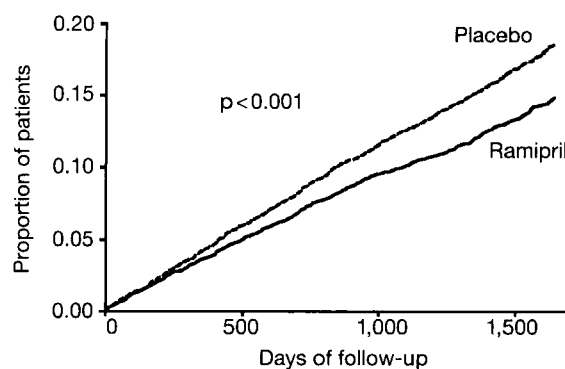


FIG. 1 Kaplan-Meier estimates of the composite outcome of myocardial infarction, stroke, or death from cardiovascular causes in the ramipril group and the placebo group. The relative risk of the composite outcome in the ramipril group compared with the placebo group was 0.78 (95% confidence interval, 0.70 to 0.86). Reprinted from Ref. No. 3 with permission. © 2000 Massachusetts Medical Society. All rights reserved.

TABLE I Incidence of secondary and other outcomes

Outcome	Ramipril group (N = 4,645)	Placebo group (N = 4,652)	Relative risk (95% CI) ^a	p Value ^b
Secondary outcomes^c				
Revascularization (%)	742 (16.0)	852 (18.3)	0.85 (0.77–0.94)	0.002
Hospitalization for unstable angina (%)	554 (11.9)	565 (12.1)	0.98 (0.87–1.10)	0.68
Complications related to diabetes (%) ^{d,e}	299 (6.4)	354 (7.6)	0.84 (0.72–0.98)	0.03
Hospitalization for heart failure (%)	141 (3.0)	160 (3.4)	0.88 (0.70–1.10)	0.25
Other outcomes				
Heart failure (%) ^d	417 (9.0)	535 (11.5)	0.77 (0.67–0.87)	<0.001
Cardiac arrest (%)	37 (0.8)	59 (1.3)	0.62 (0.41–0.94)	0.02
Worsening angina (%) ^d	1,107 (23.8)	1,220 (26.2)	0.89 (0.82–0.96)	0.004
New diagnosis of diabetes (%) ^f	102 (3.6)	155 (5.4)	0.66 (0.51–0.85)	<0.001
Unstable angina with electrocardiographic changes (%) ^c	175 (3.8)	180 (3.9)	0.97 (0.79–1.19)	0.76

^a CI denotes confidence interval.

^b p values were calculated with use of the log-rank test.

^c These events were centrally adjudicated.

^d All cases are included, whether or not hospitalization was required.

^e Complications related to diabetes include diabetic nephropathy (defined as urinary excretion of at least 300 mg/day or urinary protein excretion of 500 mg/day), the need for renal dialysis, and the need for laser therapy for diabetic retinopathy.

^f The denominator in the ramipril group is the 2,837 patients who did not have diabetes at baseline. The denominator in the placebo group is the 2,883 patients who did not have diabetes at baseline.

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primary endpoint with ramipril was 0.73 (p < 0.001). Ramipril significantly reduced the risk of reaching the primary endpoint whether or not patients were also taking aspirin or other antiplatelet agents, beta blockers, lipid-lowering drugs, or antihypertensive drugs at randomization.³

The difference between the ramipril and placebo groups in the incidence of the primary end point became significant at roughly 1 year of treatment and continued to increase for the duration of the study. In an analysis that assumed patients were still alive at the end of the preceding year, the relative risk of

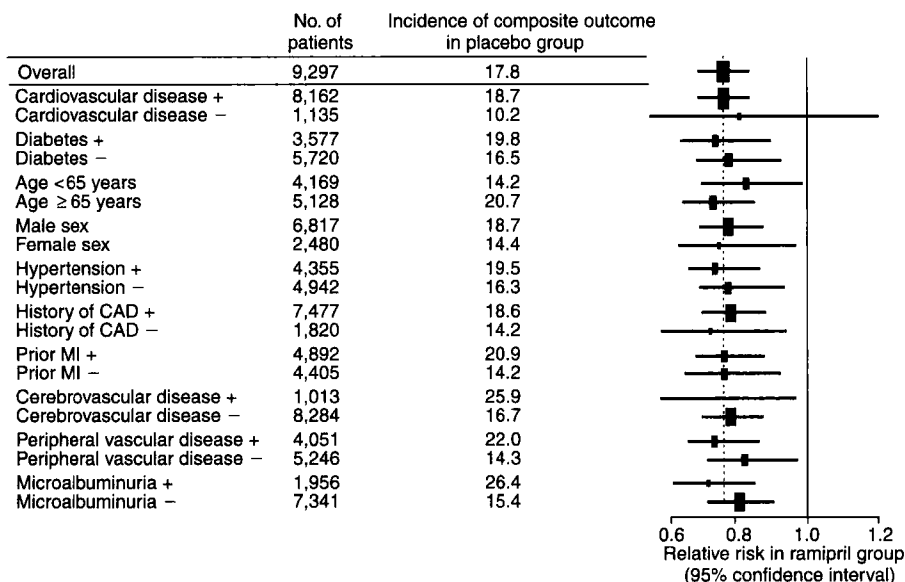


FIG. 2 The beneficial effect of treatment with ramipril on the composite outcome of myocardial infarction, stroke, or cardiovascular death, overall and in various predefined subgroups. Cerebrovascular disease was defined as stroke or transient ischemic attacks. The size of each symbol is proportional to the number of patients in each group. The dashed line indicates overall relative risk. CAD = coronary artery disease, MI = myocardial infarction. Reprinted from Ref. No. 3 with permission. © 2000 Massachusetts Medical Society. All rights reserved.

reaching the end point with ramipril was 0.78 in the second year and 0.74 in the third and fourth years.

Interpretation of the HOPE Trial Results

Whereas previous trials have proven ACE inhibition to be cardioprotective in patients with LV dysfunction,¹ the HOPE trial has shown such protection in a broad range of patients without baseline LV dysfunction. Although LV function was not routinely measured, the benefit was seen in a subgroup with a documented ejection fraction of ≥ 0.40 before randomization. The widening gap in occurrence of the primary end point between the ramipril and placebo groups at the termination of the trial points to the possibility of even greater benefit with continuing treatment.

The trial's finding that ramipril prevented diabetic complications in both the subgroup with diabetes and the overall patient population is consistent with earlier clinical evidence of similar benefit¹ and of ramipril slowing the progression of nephropathy in patients with type 2 diabetes.¹² The finding that ramipril prevents the development of diabetes is consistent with data from the Captopril Prevention Project (CAPPP) trial, which saw a lower incidence of new-onset diabetes among patients who received captopril for hypertension instead of a diuretic or a beta blocker.¹³ The possible mechanisms by which ACE inhibition may prevent diabetes or its complications include improvement of insulin sensitivity, reduction of the hepatic clearance of insulin, improvement of blood flow to the pancreas, and anti-inflammatory activity.¹⁴

In showing that ACE inhibition prevents MI and other ischemic events in a diverse at-risk population, the HOPE trial supports previous evidence^{2,9} that activation of the renin-angiotensin-aldosterone system (RAAS) is an independent risk factor for ischemic CV events. Furthermore, the trial supports earlier evidence that ACE inhibition opposes an array of ischemic processes. The temporal trend to reach the primary end point suggests a favorable effect on vascular structure. The reduction in revascularization procedures among patients taking ramipril³ is consistent with evidence that ACE inhibition reduces endothelial dysfunction and atherogenesis.²

As further evidence of the anti-ischemic potency, only a small part of ramipril's benefits was the likely result of blood-pressure reduction. In the HOPE study, only 47.6 and 46.1% of patients in the ramipril and placebo groups, respectively, had hypertension at baseline, and ramipril was associated with only a small relative reduction in blood pressure. The mean blood pressure was 139/79 mmHg at entry in both treatment groups, and at the end of the study it was 137/76 in the ramipril and 139/77 in the placebo groups. A reduction of 2 mmHg in systolic pressure might at most account for one quarter of the observed reduction in MI incidence.¹⁵ However, further prospective studies will be required to determine the relative contribution of blood pressure lowering to the beneficial effects of ramipril.

Were the benefits of ACE inhibition a class or ramipril-specific effect? The prevention of ischemic events in patients with

systolic LV dysfunction may be a class effect of ACE inhibitors, since it was observed with captopril in the SAVE trial and enalapril in both the treatment and prevention phases of the SOLVD trial.¹ However, ramipril is the only ACE inhibitor so far shown to prevent ischemic events in patients without LV dysfunction.³ The large, placebo-controlled Prevention of Events with ACE inhibition (PEACE) trial is currently assessing whether the ACE inhibitor trandolapril can prevent MI and other CV events in patients with CAD and a normal baseline ejection fraction.⁹ In the TRACE study, the initiation of therapy with trandolapril several days after MI did not prevent ischemic events, including recurrent MI or hospitalization for unstable angina, in patients with baseline CHF or LV dysfunction.^{6,9} Another large placebo-controlled study, the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA), is exploring whether the ACE inhibitor perindopril can prevent MI, unstable angina, and other CV events in patients with stable CAD and no CHF at baseline; patients with asymptomatic LV dysfunction are not excluded. Perindopril has been shown to reverse vascular endothelial dysfunction in patients with hypertension or CHF, to reduce pacing-induced ischemia in patients with CAD, and to modify atherosclerosis in pigs.¹⁶ Until results are available from either the PEACE trial or EUROPA, it would be premature to assume that the benefits of ACE inhibition in the HOPE trial are a class effect. Even if it is attributed to a class effect, the dose at which individual ACE inhibitors are effective may be considerably different. Until the data are available, the clinician would have the most confidence with ramipril 10 mg daily for the prevention of ischemic events.

Since angiotensin II-receptor blockers (ARBs) overlap with the ACE inhibitors in pharmacologic activity, can they be expected to produce the kind of anti-ischemic effects observed in the HOPE trial? The ACE inhibitors act therapeutically by blocking the formation of angiotensin II, a known or suspected promoter of vasoconstriction, aldosterone release (with resultant water and sodium retention), LV hypertrophy, atherogenic proliferation of smooth muscle in the vascular wall, and other potentially harmful processes. By contrast, the ARBs inhibit some of these processes by selectively blocking the activity of angiotensin II at the angiotensin II type 1 (AT₁) receptor. This selective blockade leads to a compensatory increase in angiotensin II levels and greater stimulation of the angiotensin II type 2 receptor, which is thought to have cardioprotective and antiatherogenic effects. The ARBs are established for the treatment of hypertension and may be superior to ACE inhibitors in tolerability.¹⁷ In addition, the ARBs have been found to prevent atherosclerosis in animals¹⁸; however, they have not yet been shown to prevent ischemic events in humans.¹⁷

Practical Conclusions

The results from the HOPE trial have the following implications for clinical practice:

1. Chronic therapy with an ACE inhibitor is appropriate for patients who were represented by the HOPE trial population in disease and/or CV risk factors.

2. Whereas it is common practice to initiate ACE inhibition routinely during the acute or subacute phase of an MI that is marked by ST-segment elevation, but to terminate such therapy after 4-6 weeks in the absence of LV dysfunction,¹ the HOPE trial makes a convincing case for continuing such therapy regardless of LV function in order to prevent recurrent ischemic events.

3. ACE inhibition can be used in a strategy for avoiding or postponing coronary angioplasty or other forms of catheter-based coronary intervention in selected patients with stable CAD. In the Atorvastatin Versus Revascularization Treatments (AVERT) trial, patients who were referred for such revascularization and had reasonable exercise tolerance, normal LV function, dyslipidemia, and single- or multivessel CAD at baseline were randomized to revascularization or lipid-normalizing therapy with atorvastatin instead.¹⁹ During a follow-up of 18 months, ischemic events occurred significantly less often and later in the atorvastatin group.²⁰ Based on this finding, the HOPE trial data, and the absence of evidence that catheter-based coronary intervention prevents ischemic CV events,³ a modification of a common approach to symptomatic CAD can be recommended. Therapy with an ACE inhibitor and a statin can be a first-line approach for patients with good exercise capacity and tolerable symptoms, and revascularization a second-line approach if exercise tolerance or symptoms subsequently worsen.

4. A case can be made for treating diabetic patients with an ACE inhibitor even in the absence of an additional CV risk factor.

5. The HOPE trial was not designed to determine whether ACE inhibition is the optimal agent for preventing CV events in high-risk hypertensive patients. This issue is being addressed in the ongoing Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), in which patients with hypertension and at least one additional risk factor for MI are randomized to an ACE inhibitor, a calcium blocker, or an alpha-adrenergic blocker.²¹ However, the HOPE trial data indicate that ACE inhibition is the logical choice for patients with hypertension and diabetes and a likely choice for patients with hypertension and vascular disease.

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