CME CREDIT

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THE HOPE STUDY

Ramipril lowered cardiovascular risk, but vitamin E did not

ABSTRACT

The Heart Outcomes Prevention Evaluation (HOPE) study found that the ACE inhibitor ramipril can lower the risk of atherosclerotic disease events and death in patients without heart failure but with known atherosclerosis or with diabetes plus at least one cardiovascular risk factor. This benefit was independent of ramipril's effect on blood pressure. Additional benefits were a reduced risk of diabetic nephropathy in diabetic patients, and a lower likelihood of newly diagnosed diabetes. On the other hand, vitamin E in the doses and duration studied (400 IU/day for 4.5 years) did not lower risk significantly.

NEARLY ALL PATIENTS with known atherosclerosis may benefit from treatment with the angiotensin-converting enzyme (ACE) inhibitor ramipril (Altace), as may diabetic patients with at least one other risk factor for coronary artery disease. These were the key findings of the recently published Heart Outcomes Prevention Evaluation (HOPE) study.[1–5]

In brief, this landmark study found that in these patient groups, 10 mg daily of the ACE inhibitor ramipril:

- Significantly reduced the incidence of death, myocardial infarction, stroke, and death from cardiovascular causes by 22%, independently of its effect on blood pressure
- Conferred benefit on almost all subgroups studied, including both sexes, diabetic patients, older patients, hypertensive patients, patients with and without prior atherosclerotic vascular disease, and patients with and without microalbuminuria
- Reduced the risk of developing type 2 diabetes mellitus in nondiabetic patients
- Reduced the risk of diabetic complications (nephropathy) in diabetic patients
- Was well tolerated.

At the same time in the same population, the study found that vitamin E had no discernible effect of significance.

This paper briefly recaps the HOPE study and puts it into perspective for practicing physicians.

Ramipril showed benefit in patients without heart failure

RATIONALE FOR THE HOPE STUDY

ACE inhibitors beneficial in heart failure

Earlier trials conclusively demonstrated that ACE inhibitors slowed the progression of heart failure and reduced mortality in patients with left ventricular dysfunction.[6–11] In addition, several showed trends toward reductions in coronary events.

For example, the Studies of Left Ventricular Dysfunction (SOLVD) trial[7] found that patients with asymptomatic left ventricular systolic dysfunction who received enalapril had a rate of cardiovascular events that was 12% lower and a mortality rate that was 8% lower than in patients who received placebo, but the trends were not statistically significant. However, a highly significant reduction in these endpoints occurred when symptomatic

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congestive heart failure was present. Overall, major coronary heart disease events were significantly reduced with enalapril.[8]

The Survival and Ventricular Enlargement (SAVE) trial,[9] in patients with left ventricular dysfunction following a myocardial infarction, found a statistically significant 19% reduction in death from all causes with the use of captopril, and a statistically significant 21% reduction in death from cardiovascular causes.

The Trandolapril Cardiac Evaluation (TRACE) study[10] evaluated 6,676 patients with left ventricular dysfunction following myocardial infarction. The time to 50% mortality was 15.3 months longer in the group taking an ACE inhibitor, and median survival was 27% longer.

On the other hand, in patients with hypertension, the Captopril Prevention Project (CAPPP)[11] found no reduction in myocardial infarctions, stroke, or other cardiovascular causes of death among captopril users compared with patients who received diuretics and beta-blockers. Confounding variables may have affected the results, however—the captopril group had higher blood pressure at baseline and more diabetic patients.

Diabetic patients with one risk factor are at high risk

Vitamin E beneficial in observational studies

As for vitamin E, laboratory data suggested that oxidized lipoproteins contribute to cellular mechanisms associated with atherosclerosis,[12–16] and data in diabetic animals suggested that vitamin E modifies this risk.[14] Furthermore, large observational studies[17,18] suggested that taking vitamin E lowered the risk for atherosclerotic events.

Aims of the HOPE study

Thus, the studies of ACE inhibitors and vitamin E raised these questions:

- Would an ACE inhibitor reduce the risk for coronary heart disease events, death, and stroke in high-risk patients without heart failure?
- Does vitamin E reduce the risk for these same events?

HOPE STUDY DESIGN

To answer these questions, the HOPE investigators devised a randomized, placebo-controlled, double-blind, two-by-two factorial design to study the ACE inhibitor ramipril 10 mg/day (vs ramipril placebo) in 9,297 patients, and vitamin E 400 IU/day (vs vitamin E placebo) in 9,541 patients. A substudy compared a low dose of ramipril (2.5 mg/day) with a full dose (10 mg/day) or placebo; there were 244 patients in this substudy group. (The results of the low-dose substudy have not yet been published; the following discussion applies only to the main study.)

Study conducted in high-risk patients

To enter the study, patients had to:

- Be at least 55 years old;
- Be at high risk for coronary events due to known atherosclerotic disease (ie, a history of coronary artery disease, stroke, peripheral vascular disease) or due to diabetes mellitus plus one other coronary risk factor (hypertension, elevated total cholesterol levels, low high-density lipoprotein cholesterol levels, cigarette smoking, or documented microalbuminuria); and
- Not have heart failure or an ejection fraction known to be lower than 40%.

Diabetic patients were included because even without known coronary disease they have approximately the same risk for heart disease events as nondiabetic patients with a history of coronary disease.[19] Furthermore, by including them, the investigators could evaluate the effects of each intervention not only on the primary outcomes, but on the microvascular complications of diabetes as well.[4,5]

A total of 9,541 patients underwent randomization at 267 centers in Canada, the United States, Western Europe, Argentina, Brazil, and Mexico. All received either vitamin E or a matching placebo. In addition, 244 received ramipril 2.5 mg/day, 4,645 received ramipril 10 mg/day, and 4,652 received a placebo matching ramipril.

Of the patients in the comparison between ramipril 10 mg/day and placebo, 2,480 were women, 5,128 were at least 65 years old, 8,160 had cardiovascular disease, 4,355 had hypertension, and 3,578 had diabetes. The ramipril and ramipril-placebo groups were well matched, as were the vitamin E and vitamin E-placebo groups.[2,3]

TABLE 1

Effect of ramipril vs placebo on outcomes in the HOPE study

OUTCOME	INCIDENCE AT 4.5 YEARS (%)		RELATIVE RISK IN RAMIPRIL GROUP	*P* VALUE
	RAMIPRIL GROUP (%) (N = 4,645)	PLACEBO GROUP (%) (N = 4,652)		
Primary outcomes				
Myocardial infarction, stroke, or death from cardiovascular cause	14.0	17.8	0.73	< .001
Death from cardiovascular cause	6.1	8.1	0.74	< .001
Myocardial infarction	9.9	12.3	0.80	< .001
Stroke	3.4	4.9	0.68	< .001
Death from noncardiovascular cause	4.3	4.1	1.03	.74
Death from any cause	10.4	12.2	0.84	.005
Secondary outcomes				
Revascularization	16.0	18.3	0.85	.002
Hospitalization for unstable angina	11.9	12.1	0.98	.68
Complications related to diabetes mellitus	6.4	7.6	0.84	.03
Hospitalization for heart failure	3.0	3.4	0.88	.25
Other outcomes				
Heart failure	9.0	11.5	0.77	< .001
Cardiac arrest	0.8	1.3	0.62	.02
Worsening angina	23.8	26.2	0.89	.004
New diagnosis of diabetes mellitus	3.6	5.4	0.66	< .001
Unstable angina with ECG changes	3.8	3.9	0.97	.76

ADAPTED FROM THE HEART OUTCOMES PREVENTION EVALUATION STUDY INVESTIGATORS. EFFECTS OF AN ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR, RAMIPRIL, ON DEATH FROM CARDIOVASCULAR CAUSES, MYOCARDIAL INFARCTION, AND STROKE IN HIGH-RISK PATIENTS. N ENGL J MED 2000; 342:145–153.

Outcomes assessed

The primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes. Each of these was also analyzed separately.

Secondary outcomes were death from any cause, the need for revascularization, hospitalization for unstable angina or heart failure, and complications related to diabetes (independent of the need for hospitalization).

Other outcomes were worsening angina, cardiac arrest, heart failure, unstable angina with electrocardiographic changes, and the development of diabetes mellitus in nondiabetic patients.

Outcomes in patients with diabetes. The same cardiovascular endpoints were assessed in diabetic patients, but outcomes measured in diabetic patients also included the onset and progression of diabetic nephropathy (albuminuria, dialysis) and retinopathy (history of laser treatment).[4]

RESULTS: RAMIPRIL VS PLACEBO

Ramipril was well tolerated and compliance was good

Ramipril was well tolerated and the patients were compliant with the treatment protocols. In the ramipril group, 82.9% of patients were still taking the medication at 1 year, 74.7% at 2 years, 70.9% at 3 years, 62.5% at 4 years, and 65.1% at the last visit.

The actual numbers of patients receiving any ACE inhibitor (including ramipril) were actually higher, with 87.4% of patients in the ramipril group taking ramipril or an open-label ACE inhibitor at 1 year, 85.1% at 2 years, 82.2% at 3 years, 75.2% 4 years, and 65.1% at the final visit. In the placebo group,

The blood pressure effect was too small to account for the degree of benefit

The HOPE trial: Ramipril reduces MIs, strokes, and cardiovascular deaths

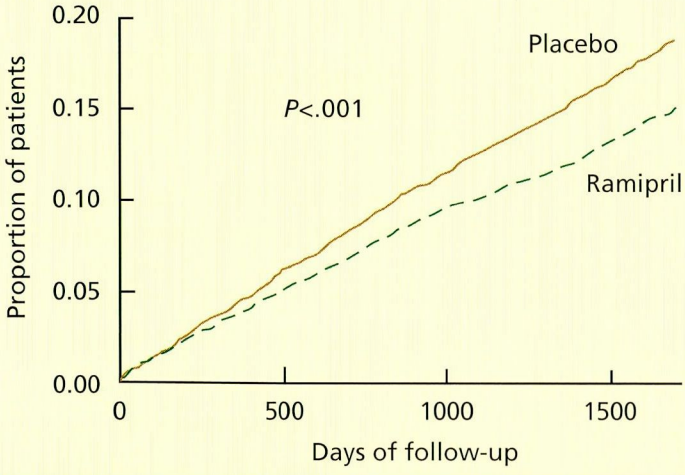

FIGURE 1. Kaplan-Meier estimates of the composite outcome of myocardial infarction, stroke, or death from cardiovascular causes among patients received ramipril 10 mg/day or placebo group in the HOPE trial. The relative risk in the ramipril group was 0.78 (95% CI 070–0.86, $P < .001$.

FROM THE HEART OUTCOMES PREVENTION EVALUATION STUDY INVESTIGATORS. EFFECTS OF AN ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR, RAMIPRIL, ON DEATH FROM CARDIOVASCULAR CAUSES, MYOCARDIAL INFARCTION, AND STROKE IN HIGH-RISK PATIENTS. N ENGL J MED 2000; 342:145–153.

TABLE 2

Subgroups of patients in whom risk for an event (composite outcome) was significantly reduced by ramipril use

Diabetes mellitus vs no diabetes mellitus
Women vs men
History of cardiovascular disease vs no history of cardiovascular disease
Age 65 years vs ≤ 65 years
Hypertension (at baseline) vs no hypertension
Presence or absence of prior atherosclerotic vascular disease
Microalbuminuria (baseline) vs no microalbuminuria

3.4% were receiving an ACE inhibitor at 1 year, 6.0% at 2 years, 8.0% at 3 years, 10.8% at 4 years, and 12.3% at the final visit.

Cough caused 7.3% of patients to stop taking ramipril, compared with 1.8% of patients receiving placebo. Hypotension or dizziness was only slightly more frequent a reason for stopping ramipril than with placebo (1.9% vs 1.5%).

Little effect on blood pressure

Ramipril had only a small effect on blood pressure. The mean blood pressure at entry was 139/79 mm Hg in both groups. At the end of the study it was 137/76 mm Hg in the ramipril group and 139/77 mm Hg in the placebo group.

Reduction in risk of cardiovascular events

At 4.5 years, 651 patients (14.0%) in the ramipril group had died of cardiovascular causes or had a myocardial infarction or stroke, compared with 826 (17.8%) in the placebo group (TABLE 1, FIGURE 1). The relative risk in the ramipril group for this primary composite outcome was 0.78 (95% CI 0.70–0.86, $P < .001$). The difference in the incidence of each of these outcomes was also statistically significant, as was the difference in all-cause mortality.

The reduction in risk with ramipril therapy was evident within 1 year after randomization, with a relative risk of 0.85 (95% CI 0.70–1.05), and it was statistically significant at 2 years with a relative risk of 0.82 (95% CI 0.70–0.94). The relative risk was 0.78 in the second year and 0.74 in the third and fourth years.

Moreover, all predefined subgroups showed a trend toward benefit, which was statistically significant in all except patients without cardiovascular disease (TABLE 2).

With respect to secondary endpoints, ramipril reduced the risk for revascularization and complications related to diabetes mellitus. Other cardiovascular endpoints reduced with ramipril included heart failure, cardiac arrest, and worsening angina.

Results of ramipril in diabetic patients

The beneficial effects of ramipril in the 3,654 diabetic patients were comparable to those seen in the trial as a whole (FIGURE 2). In addition, ramipril lowered the risk of developing overt nephropathy by 24% (95% CI 3%–40%, $P = .027$). There was no effect on diabetic retinopathy as determined by the need for laser therapy.

Lower incidence of diabetes

In the ramipril group, 102 (3.6%) of the patients developed newly diagnosed diabetes, compared with 155 (5.4%) in the placebo group (relative risk 0.66, 95% CI 0.51–0.85, $P < .001$).

LACK OF BENEFIT FROM VITAMIN E

In dramatic contradistinction to ramipril, vitamin E use had no effect on any of the atherosclerotic outcomes (FIGURE 3). The relative risk for the primary composite outcome was 1.05 (95% CI 0.95–1.16). The relative risks for the primary outcomes ranged from 1.00 to 1.17, with all 95% CIs bounding unity. Similarly, relative risks for other outcomes ranged from 1.03 to 1.17, with all CIs bounding unity.

CLINICAL IMPLICATIONS OF THE HOPE STUDY

The results of the HOPE study indicate that routine use of ACE inhibitors in patients at high risk for coronary events or stroke will reduce the risk for such events, as well as for coronary heart disease-related death. In addition, use of ACE inhibitors is likely to reduce the risk for renal disease in diabetic patients.

The reduced risk for developing diabetes mellitus in nondiabetic patients is intriguing. The data presented in the initial reports from the HOPE study do not provide the information necessary to determine whether specific demographic or clinical features will characterize which patients will get the greatest reduction in risk for developing diabetes.

The CAPPP study investigators[11] also reported a reduced risk of developing diabetes mellitus in patients receiving captopril: a relative risk of 0.86 (95% CI 0.74–0.99, $P = .039$) for all subjects and 0.78 (95% CI 0.62–0.99, $P = .041$) for those not previously treated with blood pressure medications.

Diabetic nephropathy

The beneficial effects of ramipril in reducing the risk for diabetic nephropathy are not surprising in view of the accumulating clinical trial data on the benefits of ACE inhibitors in reducing the risk for progression of diabetic nephropathy. Therefore, the HOPE study supports the use of ACE inhibitors in diabetic patients at risk for diabetic nephropathy, especially those with microalbuminuria.

The HOPE trial: Ramipril reduces MIs, strokes, and cardiovascular deaths in diabetic patients

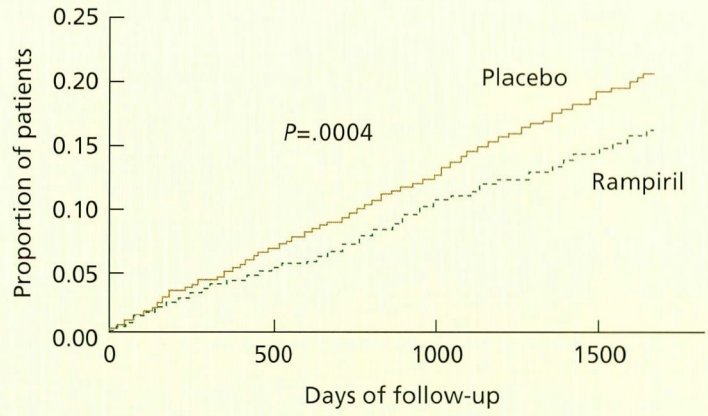

FIGURE 2. Kaplan-Meier estimates of the composite outcomes of myocardial infarction, stroke, or death from cardiovascular causes in diabetic patients receiving ramipril 10 mg/day or placebo in the HOPE trial. The relative risk reduction in the ramipril group was 25% (95% CI 12%–36%, $P = .0004$).

FROM THE HEART OUTCOMES PREVENTION EVALUATION STUDY INVESTIGATORS. EFFECTS OF RAMIPRIL ON CARDIOVASCULAR AND MICROVASCULAR OUTCOMES IN PEOPLE WITH DIABETES MELLITUS: RESULTS OF THE HOPE AND MICRO-HOPE STUDY. LANCET 2000; 355:253–259.

QUESTIONS REMAINING

How do ACE inhibitors prevent coronary events?

The exact mechanism by which ACE inhibition reduces atherosclerotic risk is uncertain.

In the HOPE study, the blood-pressure lowering effect of ramipril could account for only approximately 20% of the reduction in coronary risk and approximately 30% of the reduction in stroke risk.

The benefit may be mediated by a reduction in angiotensin II, by beneficial

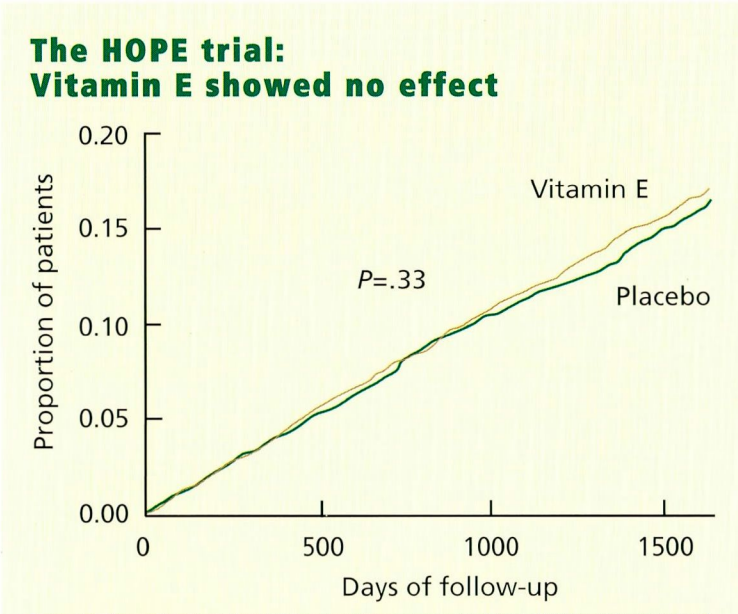

FIGURE 3. Kaplan-Meier estimates of the effect of vitamin E on the composite outcome of nonfatal myocardial infarction, stroke, or death from cardiovascular causes. The relative risk of the composite outcome in the vitamin E group as compared with the placebo group was 1.05 (95% CI 0.95–1.16, $P = .33$).

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vascular effects of increased bradykinin, or by some other mechanism. In an editorial which accompanied the article in the *New England Journal of Medicine*, Francis[20] comments that ACE inhibitors "appear to have effects on the vasculature, heart, and kidneys that go far beyond their rather small blood-pressure-lowering effects. The implication is that abrogation of the renin-angiotensin-aldosterone system at the tissue level allows the vasculature, heart, and kidneys to escape some of the ravages of long-term activity of angiotensin II and aldosterone, including growth, hypertrophy, proliferation, deposition of collagen, and tissue remodeling."

The mechanism or mechanisms by which ramipril reduced the incidence of diabetes is also uncertain. Whether ACE inhibitors reduce or alter the use of glucose-lowering medication in diabetic patients is currently under evaluation in HOPE study patients with diabetes mellitus.

Do benefits apply to all ACE inhibitors?

Would another ACE inhibitor work as well as ramipril? Ramipril (and quinapril [Accupril]) are sometimes called "tissue ACE inhibitors" because they achieve greater tissue concentrations than do many other ACE inhibitors. Whether tissue penetration is necessary for the beneficial effect cannot be determined from the HOPE study.

Two large trials (PEACE, EUROPA), using other ACE inhibitors in similar populations, may corroborate the HOPE study findings or at least help to put them in context.

Should all diabetic patients receive an ACE inhibitor?

The HOPE study does not indicate whether all diabetic patients should be considered for ACE inhibitor therapy,[21] but a strong case can be made for this approach in all patients 55 years old and older.

Vitamin E: Too little effect or too little time?

The HOPE study does not entirely exclude the possibility of beneficial effects of vitamin E on atherosclerotic events. Possibly, the duration of the study was too short to demonstrate an effect on long-term oxidative processes in atherosclerosis. Another possibility is that vitamin E must be used in combination with other antioxidants such as vitamin C. Trials are underway to address possible benefits of combination treatment. Finally, the 400-IU dose used was lower than in animal studies that showed beneficial effects on reducing oxidized lipoproteins; however, doses less than 400 IU/day have been associated with benefit in observational studies.

Other prospective trials differed in their findings: some suggested benefit[22] but others did not.[23,24] A summary of these trials[3] indicates that 50 to 400 IU of vitamin E given over periods of up to 5 years conferred no benefit.

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