ORIGINAL ARTICLE

Angiotensin-Converting–Enzyme Inhibition in Stable Coronary Artery Disease

The PEACE Trial Investigators*

ABSTRACT

BACKGROUND

Angiotensin-converting–enzyme (ACE) inhibitors are effective in reducing the risk of heart failure, myocardial infarction, and death from cardiovascular causes in patients with left ventricular systolic dysfunction or heart failure. ACE inhibitors have also been shown to reduce atherosclerotic complications in patients who have vascular disease without heart failure.

METHODS

In the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial, we tested the hypothesis that patients with stable coronary artery disease and normal or slightly reduced left ventricular function derive therapeutic benefit from the addition of ACE inhibitors to modern conventional therapy. The trial was a double-blind, placebo-controlled study in which 8290 patients were randomly assigned to receive either trandolapril at a target dose of 4 mg per day (4158 patients) or matching placebo (4132 patients).

RESULTS

The mean (±SD) age of the patients was 64±8 years, the mean blood pressure 133±17/78±10 mm Hg, and the mean left ventricular ejection fraction 58±9 percent. The patients received intensive treatment, with 72 percent having previously undergone coronary revascularization and 70 percent receiving lipid-lowering drugs. The incidence of the primary end point — death from cardiovascular causes, myocardial infarction, or coronary revascularization — was 21.9 percent in the trandolapril group, as compared with 22.5 percent in the placebo group (hazard ratio in the trandolapril group, 0.96; 95 percent confidence interval, 0.88 to 1.06; P=0.43) over a median follow-up period of 4.8 years.

CONCLUSIONS

In patients with stable coronary heart disease and preserved left ventricular function who are receiving "current standard" therapy and in whom the rate of cardiovascular events is lower than in previous trials of ACE inhibitors in patients with vascular disease, there is no evidence that the addition of an ACE inhibitor provides further benefit in terms of death from cardiovascular causes, myocardial infarction, or coronary revascularization.

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*The investigators and research coordinators who participated in the PEACE Trial are listed in the Appendix.

N Engl J Med 2004;351:2058-68.

Blockade of the renin–angiotensin system has been shown to prolong survival and reduce adverse outcomes in patients with systolic heart failure[1-3] or left ventricular systolic dysfunction.[4-9] Indeed, angiotensin-converting–enzyme (ACE) inhibitors have become a cornerstone in the treatment of these patients.[10-12] In addition, post hoc analyses of patients from the Studies of Left Ventricular Dysfunction (SOLVD)[13] and the Survival and Ventricular Enlargement (SAVE) trials,[5,14] both randomized studies that involved patients with moderate-to-severe left ventricular dysfunction, showed a reduction in the rate of acute myocardial infarction in patients who were treated with an ACE inhibitor. These observations raised the possibility that patients with coronary artery disease might benefit from ACE-inhibitor treatment, independently of their left ventricular function.

More recent studies have suggested that patients at high risk for coronary events indeed benefit from ACE-inhibitor therapy. In the Heart Outcomes Prevention Evaluation (HOPE)[15] and the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA),[16] patients with coronary or other vascular disease or with diabetes and another cardiovascular risk factor had reduced rates of death from cardiovascular causes or acute myocardial infarction when assigned to an ACE inhibitor as compared with placebo. Although both of these trials enrolled patients without a history of heart failure, many of the enrollees, especially those in the HOPE study, had an increased risk of adverse cardiovascular events.

The goal of the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial was to test whether ACE-inhibitor therapy, when added to modern conventional therapy, would reduce the rate of nonfatal myocardial infarction, death from cardiovascular causes, or revascularization in low-risk patients with stable coronary artery disease and normal or slightly reduced left ventricular function.

METHODS

The design of the PEACE Trial has been described previously[17] and is summarized here. Inclusion and exclusion criteria are shown in Table 1. This study was designed by Drs. Pfeffer, Braunwald, Domanski, Geller, and Verter. The data were held and analyzed by the clinical and statistical coordinating center under the supervision of Dr. Fowler. The manuscript was written by Dr. Braunwald, Dr. Pfeffer, and the other members of the writing committee. Drs. Fowler, Pfeffer, and Braunwald take responsibility for the data presented.

CONDUCT OF THE TRIAL

Patients underwent randomization from November 1996 to June 2000 and were followed up for as long as 7 years (median, 4.8 years), until December 31, 2003. The study was conducted after approval from the institutional review boards at 187 sites (listed in the Appendix) in the United States (including Puerto Rico), Canada, and Italy. Patients gave their written informed consent to participate. An independent data and safety monitoring board reviewed patient safety data and interim results. A morbidity and mortality review committee reviewed and classified all outcomes.

In February 2002, given the increasing evidence of the benefit of ACE inhibitors or angiotensin-receptor blockers in patients with diabetes mellitus and renal disease,[18-20] the steering committee, without knowledge of the outcome data and with approval from the data and safety monitoring board, advised the investigators to substitute open-label ACE inhibitors for the masked study treatment in patients with diabetes and either overt proteinuria or hypertension and microalbuminuria.

END POINTS

Fourteen thousand one hundred patients were required to test the hypothesis that an ACE inhibitor would reduce the rate of the original primary end point, which consisted of death from cardiovascular causes or nonfatal myocardial infarction. The secondary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or coronary revascularization. In October 1997, after 1584 patients had undergone randomization, the steering committee (without any knowledge of outcome data from the trial) concluded that recruiting 14,100 patients was not feasible and expanded the primary end point to include coronary revascularization. The sample size was reduced to 8100 patients, and the original primary end point became a secondary end point.

The study prespecified five other end points based on combinations of death from cardiovascular causes, nonfatal myocardial infarction, revascularization, unstable angina, new congestive heart failure, stroke, peripheral vascular disease, and car-

Table 1. Eligibility Criteria.*

Inclusion criteria
Age 50 yr or older
Coronary artery disease documented by at least one of the following:
Myocardial infarction at least 3 mo before enrollment
Coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty at least 3 mo before enrollment
Obstruction of ≥50% of the luminal diameter of at least one native vessel on coronary angiography
Left ventricular ejection fraction >40% on contrast or radionuclide ventriculography or echocardiography, a qualitatively normal left ventriculogram, or the absence of left ventricular wall-motion abnormalities on echocardiography†
Toleration of the medication and successful completion of the run-in phase, with ≥80% compliance with the medication
Exclusion criteria
Current use of or a current condition requiring use of an ACE inhibitor or a contraindication to ACE inhibitors
Current use of an angiotensin II–receptor antagonist
Hospitalization for unstable angina within the preceding 2 mo
Valvular heart disease deemed to require surgical intervention
Coronary-artery bypass grafting or percutaneous transluminal angioplasty within the preceding 3 mo
Planned elective coronary revascularization
Serum creatinine >2.0 mg/dl (177 μmol/liter)
Serum potassium >5.5 mmol/liter
Limited chance of 5-yr survival
Psychosocial condition precluding long-term adherence
Unable or unwilling to give consent
Female sex and of childbearing potential and not using contraception
Current use in a research trial of medication not approved by the U.S. Food and Drug Administration or the Health Protection Branch of the Canadian Department of National Health and Welfare

* ACE denotes angiotensin-converting enzyme.
† A subgroup of echocardiograms was reviewed by a core laboratory to confirm eligibility.

diac arrhythmia. In post hoc analyses, the primary end points of the HOPE[15] and EUROPA[16] studies, as well as new-onset congestive heart failure requiring hospitalization or causing death and new-onset diabetes, were also examined.

RECRUITMENT AND RANDOMIZATION

Potentially eligible subjects participated in a two-week run-in phase during which they were requested to take trandolapril (Mavik, Abbott Laboratories) at a dose of 2 mg per day. They were then excluded if their compliance was poor or if they had side effects or an abnormal rise in the serum concentration of creatinine or potassium. Consenting patients who successfully completed the run-in phase were randomly assigned to receive either trandolapril or a matching placebo; randomization was performed with the use of permuted blocks, stratified according to clinical site.

At a visit six months after randomization, patients who had tolerated the dose of 2 mg per day received a new six-month supply of study medication (trandolapril at a dose of 4 mg per day or matching placebo). Patients continued to be evaluated at six-month intervals for primary and secondary end points and for compliance with their assigned drug regimen. The patients, investigators, and staff members remained blinded to the treatment assignments.

STATISTICAL ANALYSIS

With the revised sample size, the trial had 90 percent power to detect an 18 percent relative reduction in the incidence of the primary end point, assuming a 19 percent cumulative incidence of the revised primary end point in the placebo group, when the log-rank test was used at a 0.05 level of significance. The sample-size calculation, based on the method of Shih,[21] assumed a 15 percent rate of discontinuation of active treatment and a 15 percent rate of crossover to active treatment.

The data and safety monitoring board reviewed data related to safety and the primary end point with use of the Lan–DeMets procedure[22] and an O'Brien–Fleming spending function to control the type I error[23] and recommended continuation of the trial until its scheduled conclusion. Statistical analyses of the primary and secondary end points followed the intention-to-treat principle. Relative risks, heterogeneity among strata, and interactions between treatment assignment and covariates were assessed by proportional-hazards regression.[24] All reported P values are two-sided.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Of the 8290 patients who underwent randomization, 4158 were assigned to receive trandolapril and 4132 matching placebo. All but one patient in each group began taking the assigned study medication. Eleven patients (three in the trandolapril group and eight in the placebo group) received study medication but did not return for a follow-up visit. The median follow-up period was 4.8 years in each group.

Most baseline characteristics were similar in the two treatment groups (Table 2). Overall, the patients' mean (±SD) age was 64±8 years and 18 percent were women. Fifty-five percent had had a myocardial infarction, 72 percent had undergone at least one coronary-revascularization procedure, and

Table 2. Baseline Characteristics of the Patients.*

Characteristic	Trandolapril (N=4158)	Placebo (N=4132)
Age (yr)	64±8	64±8
Age >75 yr (% of patients)	11	11
Female sex (% of patients)	19†	17
White race (% of patients)‡	92	93
Country (% of patients)		
United States and Puerto Rico	58	58
Canada	30	30
Italy	12	12
Medical history (% of patients)		
Documented myocardial infarction	54	56
Coronary disease on angiography	61	61
Angina pectoris	70	71
Percutaneous coronary intervention	42	41
Coronary-artery bypass grafting	38	40
Percutaneous coronary intervention or coronary-artery bypass grafting	72	72
Diabetes	18†	16
Hypertension	46	45
Diabetes with a history of hypertension or diastolic blood pressure ≥90 mm Hg or systolic blood pressure ≥140 mm Hg	12	11
Stroke or transient ischemic attack	7†	6
Current cigarette smoking	14	15
Blood pressure before run-in phase (mm Hg)		
Systolic	134±17	133±17
Diastolic	78±10	78±10
Diastolic blood pressure ≥90 mm Hg or systolic blood pressure ≥140 mm Hg (% of patients)	42	41
Laboratory values		
Serum creatinine (mg/dl)	1.0±0.2	1.0±0.2
Serum cholesterol (mg/dl)	192±39	192±40
Ejection fraction (%)§	58±10	58±9
Ejection fraction >40% and <50% (% of patients)§¶	15	15
Medications (% of patients)		
Calcium-channel blocker	36	35
Beta-blocker	60	60
Aspirin or antiplatelet medication	90	91
Lipid-lowering drug	70	70
Diuretic agent	13	13
Digitalis	4	4
Antiarrhythmic agent	2	2
Anticoagulant	5	5
Insulin	4	4

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.
† P<0.05 for the comparison with placebo.
‡ Race was self-declared.
§ Data on ejection fraction were available for 3952 patients in the trandolapril group and 3926 patients in the placebo group.
¶ Four patients had ejection fractions between 30 percent and 50 percent.

17 percent were known to have diabetes. A quantitative ejection fraction was available for 95 percent of the cohort, and the mean value was 58±9 percent; for the others, a two-dimensional echocardiogram was reported as showing normal left ventricular function on qualitative assessment. Seventy percent of patients were using lipid-lowering drugs. The average serum cholesterol concentration was 192 mg per deciliter (5 mmol per liter).

FOLLOW-UP

All patients were followed until the trial closeout period (July 1, 2003, to December 31, 2003), until death, or until they became lost to follow-up. Patients were considered lost to follow-up if they had not been seen at a visit within one year before the end of the study. One hundred thirty-four patients (68 in the placebo group [1.6 percent] and 66 in the trandolapril group [1.6 percent]) were lost to follow-up. Overall, vital status was known for all but 45 (0.5 percent) of the patients who underwent randomization.

COMPLIANCE

Among the patients who were randomly assigned to the trandolapril group, 81.9 percent were taking trandolapril or an open-label ACE inhibitor at one year, 78.5 percent were doing so at two years, and 74.5 percent were doing so at three years. Among the patients randomly assigned to the placebo group, 1.5 percent were receiving an ACE inhibitor at one year, 4.6 percent were doing so at two years, and 8.3 percent were doing so at three years; 68.6 percent of the treated group and 77.7 percent of the placebo group were taking the target dose of 4 mg of trandolapril or placebo, respectively, per day. Of the 2118 patients with diabetes at baseline or new-onset diabetes by February 1, 2002, 402 (19.0 percent) had taken an open-label ACE inhibitor before February 1, 2002; 286 (13.5 percent) did so for the first time after that date.

EFFECTS ON BLOOD PRESSURE

The mean blood pressure on entry into the study (before the run-in phase) was 133±17/78±10 mm Hg in the two groups combined. After 36 months, the pressure had decreased by 1.4±0.3/2.4±0.2 mm Hg in the placebo group and by 4.4±0.3/3.6±0.2 mm Hg in the trandolapril group. The changes in systolic and diastolic pressures were significantly different between the two groups at 36 months ($P<0.001$).

PRIMARY END POINT

The incidence of the primary end point was 22.5 percent in the placebo group and 21.9 percent in the trandolapril group (hazard ratio in the trandolapril group, 0.96; 95 percent confidence interval; 0.88 to 1.06; $P=0.43$) (Table 3 and Fig. 1). Adjustment for baseline characteristics (age, sex, and the presence or absence of a history of myocardial infarction, stroke or transient ischemic attack, or diabetes) did not alter the results.

No benefit in terms of the primary end point was observed among patients assigned to trandolapril in any subgroup defined according to age; sex;

Table 3. Incidence of the Primary End Point and Its Components and of Death from All Causes.*

Outcome	Trandolapril (N=4158)	Placebo (N=4132)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Primary (death from cardiovascular causes, nonfatal MI, CABG or PCI)†	909 (21.9)	929 (22.5)	0.96 (0.88–1.06)	0.43
Death from cardiovascular causes	146 (3.5)	152 (3.7)	0.95 (0.76–1.19)	0.67
Nonfatal MI	222 (5.3)	220 (5.3)	1.00 (0.83–1.20)	1.00
CABG	271 (6.5)	294 (7.1)	0.91 (0.77–1.07)	0.24
PCI†	515 (12.4)	497 (12.0)	1.03 (0.91–1.16)	0.65
Death from noncardiovascular or unknown causes	153 (3.7)	182 (4.4)	0.83 (0.67–1.03)	0.09
Death from any cause	299 (7.2)	334 (8.1)	0.89 (0.76–1.04)	0.13

* CI denotes confidence interval, MI myocardial infarction, CABG coronary-artery bypass grafting, and PCI percutaneous coronary intervention.
† PCI included laser revascularization.

race; the presence or absence of a history of myocardial infarction or of a previous revascularization procedure; the presence or absence of diabetes; the serum cholesterol or creatinine concentration; left ventricular function; or the baseline use of diuretic agents, digitalis, aspirin or antiplatelet medication, beta-blockers, calcium-channel blockers, or lipid-lowering drugs. A slight benefit was observed among patients in the trandolapril group in whom the systolic pressure before the run-in phase was less than 140 mm Hg and the diastolic pressure less than 90 mm Hg (hazard ratio as compared with placebo, 0.88; 95 percent confidence interval, 0.78 to 0.99); no benefit was observed among patients in whom the systolic pressure before the run-in phase was 140 mm Hg or higher or the diastolic pressure 90 mm Hg or higher (hazard ratio as compared with placebo, 1.09; 95 percent confidence interval, 0.94 to 1.25; P=0.02 by a test for interaction). When data for all the patients who received an open-label ACE inhibitor were censored, the hazard ratio for the primary end point in the trandolapril group was 0.95 (95 percent confidence interval, 0.89 to 1.02; P=0.16). The results did not change when data from patients with diabetes were censored at the time they began receiving ACE inhibitors on an open-label basis.

SECONDARY END POINTS AND OTHER OUTCOMES

The estimated hazard ratios for all the prespecified secondary end points in the trandolapril group, as compared with the placebo group, ranged from 0.95 to 0.98, and none were statistically significant (Table 4). Diabetes, although it was not a prespecified end point and although the analysis was not adjusted for multiple comparisons, developed in fewer of the patients assigned to receive trandolapril than of those assigned to receive placebo. In addition, fewer patients in the trandolapril group than in the placebo group were hospitalized with or died of congestive heart failure.

SIDE EFFECTS

Side effects leading to discontinuation of the study medication occurred in 6.5 percent of the patients in the placebo group and 14.4 percent of those in the trandolapril group (P<0.001). The rates of cough (39.1 percent vs. 27.5 percent, P<0.01) and syncope (4.8 percent vs. 3.9 percent, P=0.04) were greater in the trandolapril group than in the placebo group. Angioedema occurred in five patients in the placebo group (two receiving ACE inhibitors on an open-label basis) and eight patients in the trandolapril group.

DISCUSSION

In the PEACE Trial, 8290 patients with stable coronary artery disease and normal or near-normal left ventricular function were randomly assigned to receive placebo or trandolapril, and no significant differences in the primary end point — a composite of death from cardiovascular causes, nonfatal myocardial infarction, or revascularization — or in prespecified secondary end points were observed. In this trial, the ACE inhibitor trandolapril was used at the dose that had been shown in the Trandolapril Cardiac Evaluation (TRACE) Study[7] to improve survival and reduce the rate of cardiovascular events and to reduce blood pressure in trials involving subjects with hypertension.[25] Compliance with the study medication in the PEACE Trial was similar to that in other long-term trials of ACE inhibitors: slightly less than 80 percent of the patients assigned to take an ACE inhibitor and about 5 percent of those assigned to take placebo were receiving active treatment at two years. Randomization to trandolapril was associated with a clear and sustained reduction of 4.5 mm Hg in systolic pressure, as compared with randomization to placebo, in which a reduction of 1.5 mm Hg was observed. It was also associated, in a post hoc analysis, with re-

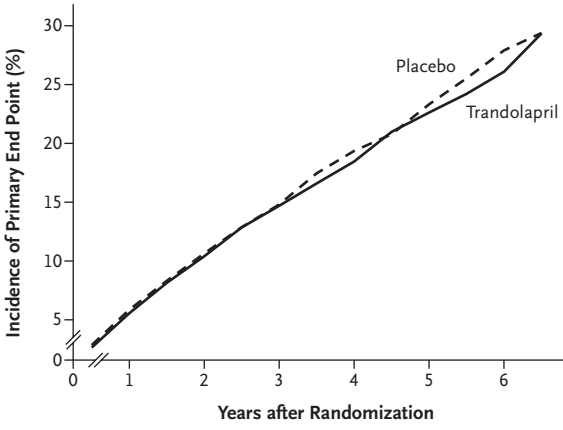

Figure 1. Cumulative Incidence of the Primary End Point, According to Treatment Group.

Table 4. Incidence of Secondary End Points and Other Outcomes.*

Outcome	Trandolapril (N=4158)	Placebo (N=4132)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Planned analyses				
Death from cardiovascular causes, nonfatal MI, revascularization, or unstable angina	1060 (25.5)	1068 (25.8)	0.98 (0.90–1.07)	0.64
Death from cardiovascular causes, nonfatal MI, revascularization, unstable angina, or new CHF	1091 (26.2)	1122 (27.1)	0.96 (0.88–1.04)	0.30
Death from cardiovascular causes, nonfatal MI, revascularization, unstable angina, new CHF requiring hospitalization, or stroke	1125 (27.1)	1164 (28.2)	0.95 (0.88–1.03)	0.23
Death from cardiovascular causes, nonfatal MI, revascularization, unstable angina, new CHF requiring hospitalization, stroke, or peripheral vascular disease requiring intervention, angioplasty, bypass surgery, or aneurysm repair	1205 (29.0)	1243 (30.1)	0.95 (0.88–1.03)	0.23
Death from cardiovascular causes, nonfatal MI, revascularization, unstable angina, new CHF, stroke, peripheral vascular disease, or cardiac arrhythmia requiring hospitalization	1284 (30.9)	1311 (31.7)	0.96 (0.89–1.04)	0.35
Death from cardiovascular causes or nonfatal MI (original outcome in PEACE Trial)	344 (8.3)	352 (8.5)	0.97 (0.83–1.12)	0.67
Post hoc analyses				
Death from cardiovascular causes, nonfatal MI, or stroke (outcome in HOPE)	396 (9.5)	420 (10.2)	0.93 (0.81–1.07)	0.32
Death from cardiovascular causes, nonfatal MI, or cardiac arrest (outcome in EUROPA)	346 (8.3)	356 (8.6)	0.96 (0.83–1.12)	0.62
CHF				
As primary cause of hospitalization or death	115 (2.8)	152 (3.7)	0.75 (0.59–0.95)	0.02
As primary cause of hospitalization	105 (2.5)	134 (3.2)	0.77 (0.60–1.00)	0.05
As primary cause of death	15 (0.4)	25 (0.6)	0.59 (0.31–1.13)	0.11
Stroke	71 (1.7)	92 (2.2)	0.76 (0.56–1.04)	0.09
Onset of new diabetes†	335 (9.8)	399 (11.5)	0.83 (0.72–0.96)	0.01

* CI denotes confidence interval, MI myocardial infarction, CHF congestive heart failure, PEACE the Prevention of Events with Angiotensin Converting Enzyme Inhibition Trial, HOPE the Heart Outcomes Prevention Evaluation,[15] and EUROPA the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease.[16]

† The analysis included 3432 patients in the trandolapril group and 3472 patients in the placebo group and excluded patients with diabetes at baseline.

ductions in the number of patients in whom diabetes developed and the number who required hospitalization for the management of heart failure, as has been observed with other ACE inhibitors.[4,18] These findings provide strong evidence of the pharmacologic activity of the standard dose of trandolapril (4 mg per day).

The SAVE[5] and the SOLVD[2,4] trials demonstrated that ACE-inhibitor therapy reduced mortality and the rate of development or intensification of heart failure in patients with symptomatic heart failure and those with asymptomatic left ventricular dysfunction. Despite the use of different ACE inhibitors and inclusion criteria, both trials reported the same intriguing secondary finding — that the rate of subsequent myocardial infarction was approximately 20 percent lower among patients randomly assigned to the ACE inhibitor than among those assigned to a placebo.[5,13,14] These results suggested that inhibition of the renin–angiotensin system may produce beneficial effects with respect to atherosclerotic events. Since both of these trials were conducted in patients with impaired left ventricular function and presumed activation of the renin–

angiotensin system, the applicability of these findings to populations of patients with normal left ventricular function remained conjectural.

Accordingly, three trials were conducted to test the hypothesis that inhibition of the renin–angiotensin system with an ACE inhibitor in patients with vascular disease who do not have overt heart failure reduces the risk of major atherosclerotic events. In HOPE, high-risk patients with vascular disease (including coronary artery disease) or diabetes who did not have heart failure and were not known to have a low ejection fraction were randomly assigned to receive either ramipril or placebo. The trial showed a significant reduction (22 percent) in the primary end point — death from cardiovascular causes, nonfatal myocardial infarction, or stroke — with ramipril.[15] Subsequently, the American Heart Association modified secondary-prevention guidelines, recommending that ACE inhibitors be "considered for all patients with vascular disease."[26]

In EUROPA, patients with stable coronary artery disease who did not have clinical evidence of heart failure and who were at a lower risk than the patients in HOPE were randomly assigned to receive perindopril or placebo.[16] The patients assigned to the ACE inhibitor had a significant reduction (20 percent) in the primary end point — death from cardiovascular causes, nonfatal myocardial infarction, or cardiac arrest. Thus, EUROPA showed that the clinical benefits of ACE inhibitors could be extended to a population of patients with coronary artery disease who had a better prognosis than those in HOPE.

In the third trial (the PEACE Trial, the subject of the current report), 8290 patients with stable coronary artery disease and normal or near-normal left ventricular function were randomly assigned to receive trandolapril or placebo; ACE-inhibitor therapy was not found to have a significant benefit. No clinical benefit was observed in the trandolapril group despite the reduction in blood pressure in that group. To interpret the predominantly negative findings of this study in the context of the positive reports from both HOPE[15] and EUROPA,[16] it is useful to compare the characteristics of the patients and the rates of events in those two trials with those in the PEACE Trial (Fig. 2). At baseline, the patients in the PEACE Trial had an average left ventricular ejection fraction of 58 percent, and their average creatinine and cholesterol concentrations were normal. Their average blood pressure at baseline was 133/78 mm Hg, which was the level

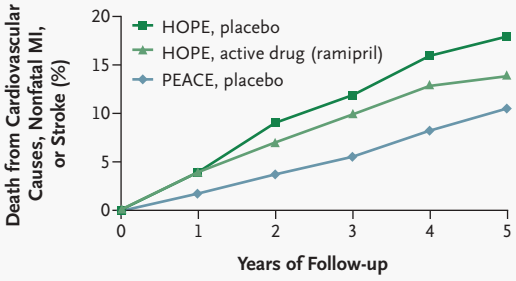

Figure 2. Comparison of Outcomes in the PEACE Trial and HOPE.

PEACE denotes the Prevention of Events with Angiotensin Converting Enzyme Inhibition Trial, HOPE the Heart Outcomes Prevention Evaluation, and MI myocardial infarction.

achieved with use of an ACE inhibitor in both HOPE and EUROPA.

The patients in the PEACE Trial also received more intensive management of risk factors than did those in HOPE and EUROPA. At baseline, 70 percent of the patients (as compared with 29 percent in HOPE and 56 percent in EUROPA) were receiving lipid-lowering therapy. Moreover, 72 percent of the patients in the PEACE Trial, as compared with 54 percent in EUROPA and 40 percent in HOPE, had undergone coronary revascularization before enrollment; this more aggressive strategy might have contributed to the lower risk of adverse events in the PEACE Trial. Therefore, it is not surprising that with more intensive treatment of coronary artery disease and risk-factor modification, adverse cardiovascular outcomes in patients assigned to placebo were substantially lower in PEACE than they were in the other two trials. Indeed, among patients assigned to take placebo, the fractions of deaths that were deemed of cardiovascular cause also reflect this difference, at 63 percent in HOPE, 59 percent in EUROPA, and 47 percent in PEACE, as compared with 35 percent in a general population matched according to age and sex with the PEACE Trial cohort.[27] Furthermore, despite objective evidence of coronary artery disease among patients in the PEACE Trial and a history of myocardial infarction in 55 percent of them, the annualized rate of death from all causes was only 1.6 percent, similar to that of an age- and sex-matched general population.[27]

Thus, we hypothesize that the PEACE Trial does not demonstrate the benefits of ACE inhibition

shown by HOPE and EUROPA because the patients enrolled in the PEACE Trial were at lower risk for cardiovascular events. This conclusion can be attributed in part to their baseline characteristics, including the documented absence of clinically significant left ventricular dysfunction as well as the prior use of procedures and therapies and in part to ongoing medical management. Indeed, the event rates in the placebo group in the PEACE Trial were not only lower than those in the placebo groups in HOPE or EUROPA; they were also lower than the event rates in the ACE-inhibitor groups in those two previous trials.

The PEACE Trial demonstrates that in a population of patients with coronary artery disease and preserved ejection fraction who receive intensive current standard therapy, usually including coronary revascularization and lipid-lowering agents, and in whom the rate of cardiovascular events is therefore already quite low, there appears to be no evidence of cardiovascular benefit from the addition of ACE inhibitor therapy. Therefore, ACE inhibitors may not be necessary in all such patients to reduce the risk of death from cardiovascular causes, nonfatal myocardial infarction, or coronary revascularization. However, physicians may still wish to consider ACE-inhibitor therapy for any patient who does not clearly fit the profile of patients in this trial.

Supported by a contract (N01HC65149) from the National Heart, Lung, and Blood Institute and by Knoll Pharmaceuticals and Abbott Laboratories, which also provided the study medication.

Dr. Braunwald reports having received research grant support and lecture fees from Bristol-Myers Squibb and Merck; Dr. Hsia grant support from Novartis; Dr. Pfeffer grant support and lecture fees from Novartis, as well as lecture fees from Bristol-Myers Squibb and Pfizer; and Dr. Rouleau consulting fees from Novartis and lecture fees from Pfizer and Novartis. Brigham and Women's Hospital has been awarded patents regarding the use of inhibition of the renin–angiotensin system in selected survivors of myocardial infarction; Drs. Pfeffer and Braunwald are among the coinventors. The licensing agreement with Abbott and Novartis is not linked to sales.

APPENDIX

The following investigators and research coordinators participated in the PEACE Trial (the complete list is available at http://www.bsc.gwu.edu/peace/): *Executive Committee* — E. Braunwald (co-chair), M.A. Pfeffer (co-chair), M. Domanski, S. Fowler, M. Rice, Y. Rosenberg; *Steering Committee* — Members of the Executive Committee and M. Dunlap, G. Flaker, N. Geller, B. Gersh, A. Goldberg, J. Hsia, M. Limacher, A. Maggioni, P. Mills, J. Rouleau, J. Warnica, A. Wasserman; *Sponsor* (National Heart, Lung, and Blood Institute, Bethesda, Md.) — M. Domanski (project officer), Y. Rosenberg (co–project officer), N. Geller, P. Mills; *Clinical and Statistical Coordinating Center* (George Washington University, Rockville, Md.) — S. Fowler (principal investigator), P. Cleary, N. Close, T. Davey, J. Green, J. Hsia (Washington, D.C.), K. Jablonski, D. Mason, S. Pakalapati, M. Rice, J. Verter, A. Wasserman, J. Weir, V. 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Poulin; London Health Sciences Centre, London — M. Arnold, M. Krupa; Centre Hospital de la Region de l'Amiante, Thetford Mines — M. Boulianne, J. Campeau, F. Ouimet, B. Roberge; Montreal General Hospital, Montreal — T. Huynh, S. Finkenbine, B. St. Jacques, C. Boudreault; Brampton Research Associates, Brampton — D. Borts, N. Bonafede, J. Burtcher, C. Edwards; Dr. R.S. Baigrie, Sudbury — R. Baigrie, F. Gee, J. Judge, K. Reilly; Vancouver Hospital and Health Sciences Centre, Vancouver — V. Bernstein, K. MacDonald, S. Mooney; Laval Hospital, Ste.-Foy — J. Rouleau, R. Vienneau; Lakeshore General Hospital, Pointe-Clair — J.-P. Mayer, S. Mitges; Neureka Research Incorporated, Sudbury — S. Nawaz, R. Dhaliwal; Centre Hospitalier Affilié Universitaire de Québec Pavillion Enfant Jesus, Quebec — P. Talbot, M. Talbot; Health Sciences Centre, St. John's — B. Sussex, S. Newman; University of Ottawa, Ottawa — M. Baird M. Fraser; Hôp. Notre-Dame, Montreal — C. Guimond, J. Leboeuf; St. Michael's Hospital, Toronto — G. Moe, D. Day; Innovative Cardiac Care, Saskatoon — G. Rajakumar, B. Kroeger; Saskatoon — M. Khouri, N. Zello; Group Health Centre, Sault Ste. Marie — H. Lee, K. Barban; London Health Sciences Centre-University Campus, London — W. Kostuk, A.-M. Powell; Royal Victoria Hospital, Montreal — M. Smilovitch, V. Toyota; Centre Hospitalier de l'Université de Montréal (CHUM), Hotel-Dieu, Montreal — D. Phaneuf, R. Duclos; Hop. Saint-Luc Du CHUM, Montreal — G. Goulet, L. Primeau; Windsor — T. Machel, J. Morash; Hôpital Maisonneuve-Rosemont, Montreal — D. Gossard, L. Boutin; Cambridge — S. Vizel, B. Fox; St. Joseph's Hospital, Hamilton — E. Stanton, M. Lawrence; Sullivan Cardiology Associates, Hamilton — H. Sullivan, R. Paterson; Odyssey Research Services, Victoria — G. Hoag, K. Ilott; Prince George Regional Hospital, Prince George — J. Dufton, R. Sweeney. **Puerto Rican Clinical Centers** (in order of enrollment): University of Puerto Rico, San Juan — M. Garcia-Palmieri, H. Banchs, M. Gonzalez, M. Perez; Centro Cardiovascular de Caguas, Caguas — P. Colon, Sr., N. Vazquez. **Italian Clinical Centers** (in order of enrollment): Ospedale Civile, Passirana-Rho — C. Schweiger, A. Frisinghelli; Ospedale Cardinale Panico, Tricase — A. Galati, P. Palma; Ospedale G.F. Ingrassia, Palermo — P. Di Pasquale, F. Clemenza; Ospedale San Bartolomeo, Sarzana — G. Filorizzo, R. Petacchi; Ospedale di Circolo Zappatoni, Cassano d'Adda — R. Cogo, M. Ferrari; Presidio Ospedale Villa Sofia, Palermo — A. Battaglia, F. Mancino; Ospedale Civile, Policoro — B. D'Alessandro, L. Truncellito; Pres Ospedale S. Maria della Speranza, Battipaglia — M. Maina, S. Romanzi; Ospedale S. Sebastiano di Caserta — C. Chieffo, A. Cardillo; Ospedale Ignazio Veris Delli Ponti, Scorrano — E. De Lorenzi, A. Bergarno; Ospedale Cardarelli, Napoli — A. Boccalatte, G. Gaeta; Presidio Ospedale, Montebelluna — G. Neri, G. Masaro; Policlinico Catanzaro, Catanzaro — F. Perticone, R. Maio; Ospedale Riuniti, Foggia — M. De Biase, M. Carrone; Fondazione S. Maugeri Clinica del Lavoro, Cassano delle Murge — D. Scrutinio, R. La Gioia; Ospedale Civile, Lanciano — L. Leonzio, D. Tullio; Ospedale Generale di Zona Valduce, Como — M. Santarone, L. Tagliagambe; Presidio Ospedale, Rovigo — P. Zonzin, M. Capanna; Ospedale A. Ajello, Mazara Del Vallo — N. Di Giovanni, I. Fiore; Ospedale Riuniti, Bergamo — A. Gavazzi, D. Mazzoleni; Ospedale Bellaria, Bologna — G. Pinelli, M. Ribani; Ospedale Garibaldi, Catania — S. Mangiameli, V. Rubino; Ospedale L. Sacco, Milan — M. Viecca, R. Sala; Ospedale San Michele Brotzu, Cagliari — M. Porcu, S. Salis; Ospedale S. Maria Della Pietà, Camerino — R. Amici, G. Patteri; Ospedale Civile Mellini, Chiari — F. Bortolini, A. Turelli; Ospedale Civile Santa Maria Delle Croci, Ravenna — A. Maresta, G. 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