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A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

ACE Inhibition in Patients with Coronary Artery Disease Results of the Trio of Trials, including the Late-Breaking Results of the Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) Trial

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Reported and discussed by:
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The renin-angiotensin-aldosterone system (RAAS) plays a key role in the development and progression of coronary artery disease (CAD). Angiotensin-converting enzyme (ACE) inhibitors are established therapy for patients with chronic heart failure and systolic left ventricular (LV) dysfunction, as well as following myocardial infarction (MI) complicated by LV dysfunction and/or clinical heart failure. Since the early 1990s, three independent large-scale trials have been designed to test whether an ACE inhibitor reduces major cardiovascular (CV) events in populations with normal LV function that have, or are at high risk of, coronary or other vascular disease. Results of the latest of the "trio of trials," the Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial were recently presented and published. This issue of *Cardiology Scientific Update* reviews the clinical implications of the results of the PEACE trial in the context of the 2 previously published trials.

The RAAS plays an intimate role in the progression of the CV disease continuum, from the first appearance of risk factors, to the development of atherosclerosis and, ultimately, the damage of vital organs.[1,2] ACE inhibitors have been shown to reduce mortality in patients with congestive heart failure accompanied by LV dysfunction,[3,4] as well as in patients with MI complicated by LV dysfunction and/or heart failure.[5-8] As a result, ACE inhibitors now constitute standard therapy in these patients.

Analyses from both the Survival and Ventricular Enlargement (SAVE) trial, as well as the Studies Of Left Ventricular Dysfunction (SOLVD) trial, indicate that ACE inhibitor use can reduce the incidence of major coronary events,[9,10] suggesting that an ACE inhibitor may exert antiatherosclerotic and antiischemic effects in patients with LV systolic dysfunction. Indeed, the experimental evidence for these ACE inhibitor effects is strong. ACE inhibitors, by decreasing angiotensin II and/or increasing bradykinin, decrease vascular nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, reactive oxygen species (ROS), nitric oxide destruction, and endothelial dysfunction. ACE inhibitors have also been shown to prevent arterial nuclear factor-kappa B activation and monocyte chemoattractant protein-1 expression, and reduce leukocyte migration into vessel walls, foam cell formation, and atherosclerosis. In addition, these agents decrease metalloproteinase 2 and 9 activity and improve plaque stability and fibrinolytic balance.[11-15] Recently, ACE inhibitors have been shown to decrease activities of the lectin-like oxidized LDL (LOX-1) receptors, which mediate

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the oxidation of LDL-cholesterol and ROS production.[16] This same mechanism appears to be shared by the statins as well.[17]

The above clinical and experimental observations notwithstanding, until recently, it was still unclear whether the benefits of ACE inhibition extended to patients with stable CAD, but normal LV systolic function who, with conventional risk factor modification, would presumably be at a lower risk for adverse CV events. To address this issue, beginning in 1993, 3 independent large-scale trials were initiated to test whether an ACE inhibitor reduces major CV events in populations with, or at high risk of, coronary or other vascular disease.[18-20]

The HOPE trial

The first of the "trio of trials" – the Heart Outcomes Prevention Evaluation (HOPE) trial – compared the effects of ramipril 10 mg/day (administered in the evening) with placebo in 9,297 patients deemed at high risk for CV events by evidence of either vascular disease or diabetes accompanied by one other CV risk factor.[20] To be recruited to HOPE, patients could not have heart failure or a low LV ejection fraction (if known).

Patients were recruited between December 1993 and June 1995 with a fairly large representation from Canadian centres. The study was terminated earlier than planned, in March 1999, because of clear evidence of benefit from active treatment. The primary outcome, a composite of CV death, MI, and stroke was reduced by 22% ($p<0.0001$). Each component of the primary outcome was also significantly reduced. All-cause mortality was reduced by 16% ($p=0.05$). Furthermore, there were significant reductions in new-onset diabetes, new-onset heart failure,[21] as well as the need for revascularization procedures. Systolic blood pressure (SBP) was lower by 3.3 mm Hg in the ramipril-treated group when compared to the placebo-treated group. Extended follow-up of a subset of the HOPE study demonstrated the persistence of benefit over the long-term with ACE inhibition and further benefits were demonstrated in the prevention of MI and new-onset diabetes.[22]

A recent economic analysis employing a third-party perspective (Medicare for the United States and Ministry of Health for Canada) indicated a dominant strategy with 90% of cases falling either into a cost-neutral or cost-saving situation with up to 4.5 years of treatment and substantial health benefits.[23]

The EUROPA trial

The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) was a multicentre European trial that involved 424 centres in 24 countries that compared the effects of perindopril 8 mg daily with placebo, added to standard therapy in 12,218 patients with CAD.[18,24] Enrolled patients could not have a history of heart failure, but documentation of LV systolic function was not required for study entry. The primary study endpoint was combined CV mortality, non-fatal MI, and resuscitated cardiac arrest. The secondary endpoints included a composite of all-cause mortality, non-fatal MI, hospitalization for unstable angina, and resuscitated cardiac arrests, as well as admission for heart failure, revascularization, and stroke.

Results of the EUROPA trial have been reviewed in previous issues of *Cardiology Scientific Update*. Patients were recruited between October 1997 and June 2000. A higher proportion of patients in EUROPA than in the HOPE study received contemporary background therapy. Indeed, the annualized event rate for the composite primary endpoint was only 2.4%, suggesting that patients in EUROPA were not as high-risk as those in HOPE. Compared to placebo, the primary endpoint – CV death, non-fatal MI, and resuscitated cardiac arrest – was reduced by 10%, 11%, and 14% after the first, second, and third year, respectively, post-randomization. The differences reached statistical significance by the third year. The relative risk reduction over 4.2 years of follow-up was 20% ($p=0.0003$).

Systolic blood pressure (BP)/diastolic BP was 5 mmHg/2 mmHg lower in the perindopril-treated group. However, recent unpublished *post hoc* analyses suggest that the benefit of ACE inhibition could not be explained entirely by BP differences.

The PEACE trial

The Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial was designed to test whether ACE-inhibitor therapy with trandolapril, when added to modern conventional therapy, would reduce death from CV causes, the rate of nonfatal MI, or the need for revascularization in low-risk patients with stable CAD disease and documented normal or slightly reduced LV systolic function. The design of the study has been published previously.[19] The PEACE trial was funded by the National Heart, Lung, and Blood Institute, with study medications provided by Abbott Laboratories (formerly Knoll AG). Trandolapril was chosen by the investigators because it was the only ACE inhibitor administered once daily that was shown to reduce all-cause mortality in patients with MI complicated by LV dysfunction.[7] The main inclusion criteria were:

- Age ≥ 50 years
- CAD as documented by at least 1 of the following:
  – MI at least 3 months before enrollment

Figure 1: Patient flow of PEACE

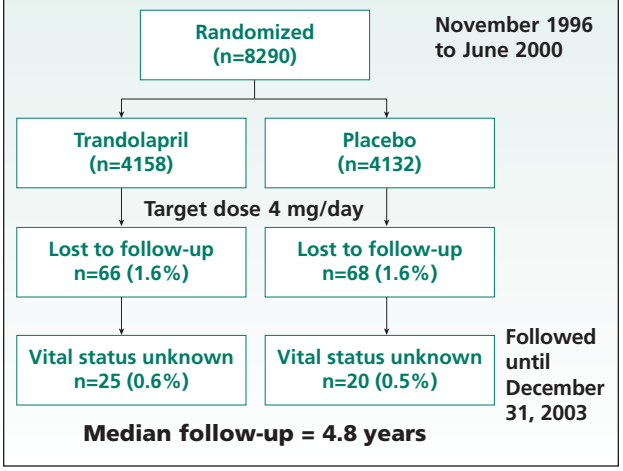


Table 1: Baseline characteristics of patients from HOPE, EUROPA, and PEACE

Characteristic % (unless otherwise specified)	HOPE n = 9297	EUROPA n = 12218	PEACE n = 8290
Mean age	66	60	64
Prior MI	53	65	55
Diabetes mellitus	38	12	17
Prior CABG/PCI	40	55	72
Mean LV ejection fraction	N/A	N/A	58
Mean SBP/DBP (mm Hg)	139/79	137/82	133/78
Aspirin/antiplatelet drugs	76	92	91
Lipid-lowering drugs	29	58	70
Beta-blockers	40	62	60

MI = myocardial infarction; CABG/PCI = coronary artery bypass graft surgery/percutaneous coronary intervention; SBP/DBP = systolic and diastolic blood pressure

– coronary artery bypass graft surgery or percutaneous coronary intervention angioplasty at least 3 months before enrollment
– ≥50% obstruction of the luminal diameter in at least 1 native vessel on coronary angiography
– LV ejection fraction >40% on contrast or radionuclide ventriculography or echocardiography, a qualitatively normal left ventriculogram, or the absence of LV wall-motion abnormalities on echocardiography

It should be noted that in PEACE, the documentation of normal LV ejection fraction (>40%) was mandatory; however, this was not required in the HOPE and EUROPA trials. Patients were recruited from the United States, including Puerto Rico (118 clinics, 4817 patients), Canada (32 clinics, 2513 patients), and Italy (37 clinics, 960 patients). The primary composite endpoint for PEACE was CV death, non-fatal MI, and the need for coronary revascularization. The study pre-specified 5 other endpoints based on combinations of CV death, nonfatal MI, revascularization, unstable angina, new heart failure, stroke, peripheral vascular disease, and cardiac arrhythmias. Post hoc analyses included the primary endpoints of the HOPE and EUROPA studies,[20,24] and new congestive heart failure requiring hospitalization or causing death, as well as new-onset diabetes. The planned number of recruits in PEACE was 8100, which assumed 90% power with (α of 0.05, 18% RR of the primary endpoint, 19% cumulative event rate of the primary endpoint in the placebo group, 15% discontinuation of study drug on active treatment, and 15% crossover to open-label ACE inhibitor therapy in the placebo group.

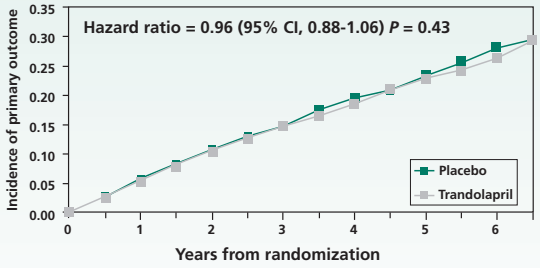
Results of the PEACE study were recently presented and published.[25] The patient flow of PEACE is shown in Figure 1.

Randomization began in November 1996 and ended in June 2000. Patients were followed up for as long as 7 years (a median of 4.8 years). Follow-up was close to complete. Baseline characteristics were similar for trandolapril- and placebo-treated patients for almost all of the parameters. For the purpose of subsequent discussion, selected baseline characteristics of the 2 treatment groups combined are shown in Table 1, along with those from HOPE and EUROPA.

When compared to HOPE, at baseline, the PEACE study cohort had less diabetes and a much higher use of antiplatelet agents. Of the 3 studies, the PEACE cohort had the lowest SBP, but the highest rate of previous coronary revascularization and use of lipid-lowering therapy. After 36 months, trandolapril reduced SBP and DBP by 4.4 and 3.6 mm Hg, respectively. These decreases were significantly greater than those in the placebo group (1.4 and 2.4 mm Hg, respectively, $p<0.001$). In the trandolapril group, 82% were taking trandolapril or an open-label ACE inhibitor at 1 year, 79% at 2 years, and 75% at 3 years. In the placebo group, 2% were receiving an ACE inhibitor at 1 year, 5% at 2 years, and 8% at 3 years. Sixty-nine percent of the trandolapril group and 78% of the placebo group were taking the target dose of 4 mg of the study medication.

Data on the primary endpoint and its components are shown in Figure 2 and Table 2. There were no differences in the primary endpoint or any of its components between the trandolapril and placebo groups. All-cause mortality – 7.2% in trandolapril group and 8.1% in placebo group – was also not different (hazard ratio 0.89, 95% CI, 0.76-1.04, $p=0.13$).

Figure 2: Primary outcome of PEACE: CV death, MI, CABG/PCI



Number of patients							
Placebo	4132	3992	3722	3491	3034	1941	906
Active	4158	4019	3758	3515	3093	1981	985

Analyses of pre-defined subgroups revealed no significant influence on the primary outcome by age, gender, prior revascularization, history of diabetes, and LV ejection fraction. The pre-specified secondary endpoints (consisting of different combinations of CV death, non-fatal MI, revascularization, unstable angina, new heart failure, stroke, peripheral vascular disease, and cardiac arrhythmias), were not different (data not shown). Data from the post-hoc analyses are shown in Table 3. In this regard, hospitalization from heart failure, as well as hospitalization and death primarily from heart failure, were lower in the trandolapril group, as was new-onset diabetes.

The study medications were well-tolerated. Side effects leading to discontinuation occurred in 6.5% of the placebo group and 14.4% of the trandolapril group ($p<0.001$). Cough was more frequent in the trandolapril group (39.1% vs. 27.5%, $p<0.01$). Angioedema was uncommon, occurring in 5 subjects (2 on open-labeled ACE inhibitors) and 8 subjects in the trandolapril group.

Discussion and clinical implications of the PEACE trial

Results of the PEACE trial, the last of the "trio of trials," demonstrate that in patients with stable CAD (ie, patients with documented normal LV systolic function) and a majority who received close to maximal contemporary therapy (including revascularization and antiplatelet and lipid-lowering therapy), the addition of an ACE inhibitor does not produce an incremental benefit in reducing CV death, non-fatal MI, and the need for revascularization.

Table 2: Primary endpoint and its components

Outcome	Trandolapril n=4158 %	Placebo n=4132 %	Hazard ratio (95% CI)	*P*-value
CV death, MI, CABG or PCI	21.9	22.5	0.96 (0.88-1.06)	NS
CV death	3.5	3.7	0.95 (0.76-1.19)	NS
Non-fatal MI	5.3	5.3	1.00 (0.83-1.20)	NS
Revascularization	17.8	18.0	0.98 (0.88-1.08)	NS

MI = myocardial infarction; CABG/PCI = coronary artery bypass graft surgery/percutaneous coronary intervention; CV = cardiovascular

The findings from PEACE differ from those of HOPE and EUROPA where it was observed that ACE inhibition provided a benefit on CV outcomes.[20,24] There are 2 possible explanations for the lack of effect on the primary outcome with trandolapril in PEACE. First, some may argue that trandolapril was not the appropriate ACE inhibitor to use (ie, the cardioprotective property of the ACE inhibitor is not a "class effect") or that the proper dose of trandolapril was not employed in PEACE. This, however, is highly unlikely, given the fact that trandolapril administered at the dose employed in PEACE has been known to be an effective antihypertensive agent,[26] and shown to reduce all-cause, as well as CV mortality, in patients following MI.[7,27] Furthermore, in the PEACE

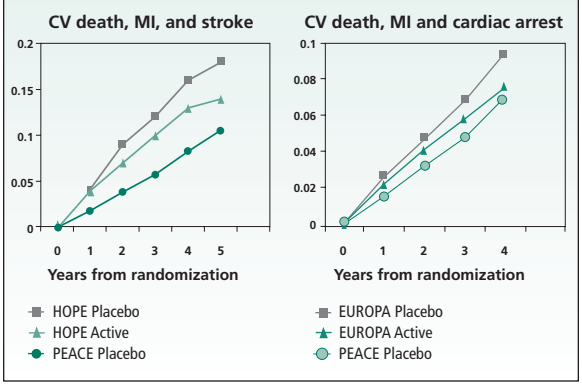
Table 3: Selected post hoc analyses

Outcome	Trandolapril n=4158 %	Placebo n=4132 %	Hazard Ratio (95% CI)	*P*-value
CHF hospitalization	2.5	3.2	0.77 (0.60-1.00)	0.048
CHF hospitalization or CHF death	2.8	3.7	0.75 (0.59-0.95)	0.018
Stroke	1.7	2.2	0.76 (0.56-1.04)	0.09
New diabetes†	9.8	11.5	0.83 (0.72-0.96)	0.014
CV death, non-fatal MI, or stroke (outcome in HOPE)	9.5	10.2	0.93 (0.81-1.07)	0.32
CV death, non-fatal MI, or cardiac arrest (outcome in EUROPA)	8.3	8.6	0.96 (0.83-1.12)	0.62

CHF= congestive heart failure; MI=myocardial infarction; CV= cardiovascular

† Analysis included 3432 patients in the trandolapril group and 3472 patients in the placebo with no diabetes at baseline

Figure 3: Comparison of outcomes of PEACE with HOPE and EUROPA



trial, trandolapril reduced BP to a similar degree as the other ACE inhibitors in HOPE and EUROPA and some of the endpoints, such as new-onset diabetes and heart failure hospitalizations, were significantly reduced. These observations, therefore, strongly suggest that trandolapril at 4 mg daily exerted pharmacologic effects.

The second and most plausible explanation was that the PEACE study had the lowest-risk patient population of the 3 trials so that, in PEACE, no incremental benefit from ACE inhibition accrued. The hypothesis that PEACE was a low-risk population is supported by the following observations:

- As discussed earlier, of the 3 trials, patients in PEACE were receiving the most contemporary conventional therapy and management of risk factors. This included the highest proportion of patients with prior revascularization, the best-controlled BP, and the widest use of lipid-lowering agents.
- PEACE was the only study in which documentation of normal LV systolic function was required for trial entry. Indeed, the annualized CV mortality rate of the placebo group in HOPE, EUROPA, and PEACE was 1.62%, 0.97% and 0.77% respectively.
- The annualized all-cause mortality for the placebo group in PEACE was 1.6%, which is comparable to an age- and gender-matched general population in the U.S.[28] In this regard, it is useful to compare the event rate for the PEACE cohort with those of HOPE and EUROPA, using the primary endpoints of the 2 older trials. As shown in Figure 3, the placebo event rate for CV outcomes in the PEACE cohort was consistently lower than even the ACE inhibitor-treated patients in the HOPE (left panel), as well as in the EUROPA trial (right panel). In terms of absolute reduction, the projected number of patients needed to treat for 4 to 5 years in order to prevent one CV death progressively increases from higher to lower risk patients, from 50 in HOPE, 170 in EUROPA, to 500 in PEACE.

What are the clinical implications of the PEACE study results? Clinicians need to be more discriminating when they are making decisions about prescribing ACE inhibitors to patients with stable CAD. For patients who clearly fit into the PEACE population – the characteristics are reviewed in this issue of *Cardiology Scientific Update* – treatment with an ACE inhibitor is not indicated. On the other hand, depending on geographic locations and practice patterns, a sizeable number of patients with presumed stable CAD will likely continue to be at high risk for CV events, including those with CAD, but with unknown LV systolic function and those with no revascularization and inadequate control of diabetes, BP, and cholesterol. In these patients, ACE inhibitors will continue to have an important role in their management.

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