

Report from the **American Heart Association Scientific Session**  
Orlando, Fl., 2004



# EXPERT OPINIONS.MR

CLINICAL IMPACT.

MEETING REPORT

Expert Opinions is published by E.O.C.I. Pharmacomm Ltd.

faculty



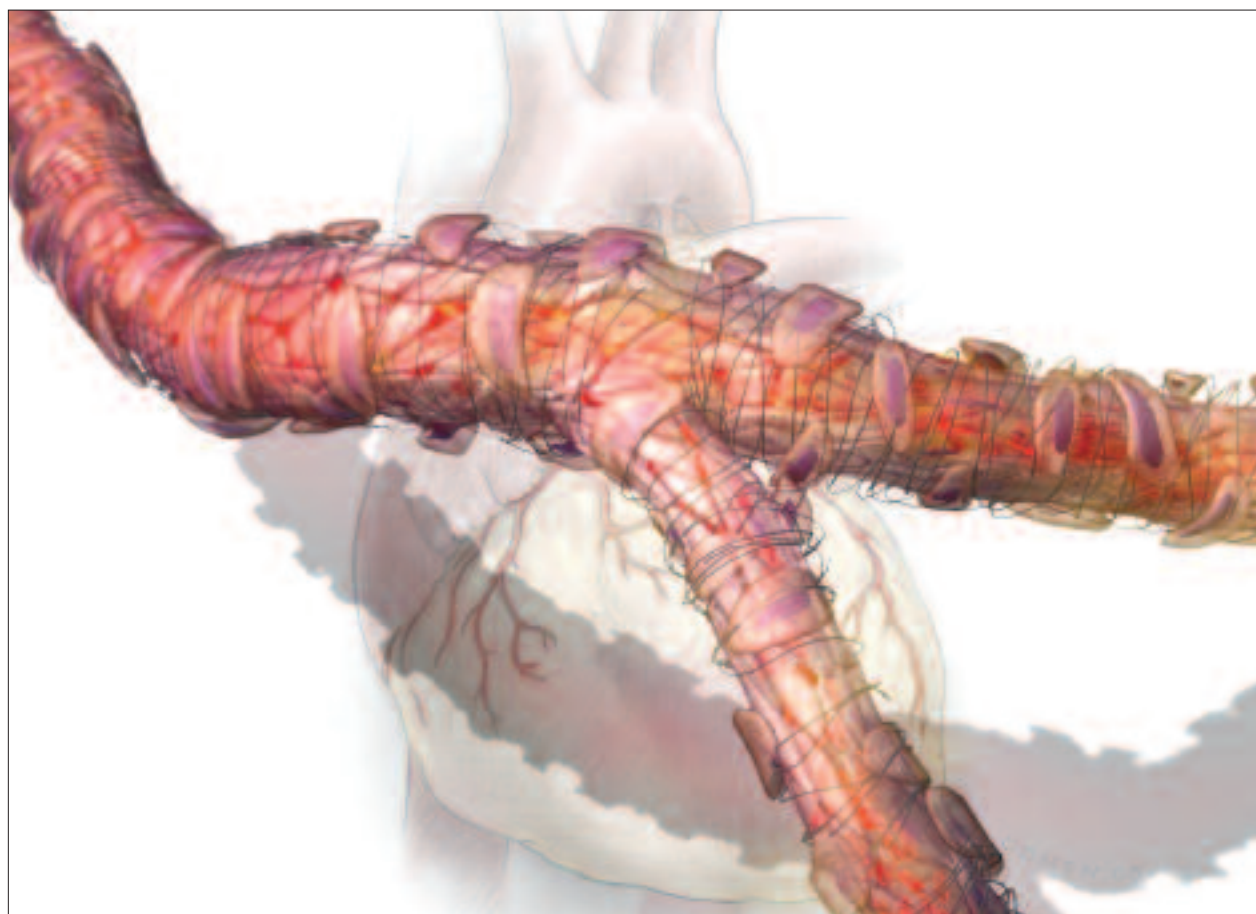
**Milan Gupta, MD**  
McMaster University  
Hamilton, ON



**Subodh Verma, MD, PhD**  
University of Toronto  
Toronto, ON



**George Honos, MD**  
McGill University  
Montreal, QC



## The PEACE Study in Perspective: Acknowledging the ACE Inhibitor Ancestry

Volume 1, number 8

For more information please contact

[info@eocipharma.com](mailto:info@eocipharma.com)

Publications Mail Agreement Number 40816046 Canada Post: Please return undeliverable mail blocks to:  
4020 Saint-Ambroise Street, Suite 495, Montreal, QC H4C 2C7

Captopril, the first angiotensin-converting enzyme (ACE) inhibitor, entered clinical trials in 1977 and was approved by the FDA in 1981 as an antihypertensive agent. Blockade of the renin-angiotensin-aldosterone system with ACE inhibitors thereafter became an attractive target in patients with systolic heart failure. This hypothesis was extensively evaluated through a series of clinical trials in the early-to-mid 1990s, including SAVE,<sup>1</sup> SOLVD,<sup>2,3</sup> AIRE<sup>4</sup> and TRACE.<sup>5</sup> These studies, in patients with either symptomatic heart failure or with asymptomatic left ventricular dysfunction, each demonstrated an impressive 20% reduction in total mortality with various ACE inhibitors, including captopril, enalapril, ramipril, and trandolapril. As a result, ACE inhibition rightfully became a cornerstone of therapy in heart failure.

An unexpected finding in all of these studies, however, was an approximate 20% reduction in the risk of myocardial infarction (MI). When these studies were conducted over a decade ago, ACE inhibitors were not known to be anti-ischemic, and were expected to have a neutral effect on the risk of MI. Since a reduction in MI did not fit with the postulated mechanisms of action of ACE inhibitors, further study was warranted. Additionally, although ACE inhibition clearly improved prognosis in subjects with left ventricular dysfunction, their role in patients with coronary disease and preserved left ventricular function was still untested.

To answer these important questions, three separate trials of ACE inhibition in patients with preserved LV function and cardiovascular disease were independently designed and conducted in parallel, beginning in the mid 1990s. The first trial completed was the HOPE study, which compared ramipril 10 mg to placebo in high-risk subjects over the age of 54 who had either established

**There was an 11% relative risk reduction in all-cause mortality associated with trandolapril, which is consistent with other trials of ACE inhibition (HOPE and EUROPA), although this did not reach statistical significance ( $p=0.13$ ).**

vascular disease or diabetes, with at least one additional risk factor.<sup>6</sup> The HOPE study demonstrated a highly significant 22% reduction in the composite endpoint of CV death, MI and stroke. Subsequently, the EUROPA trial, in patients with CAD aged 18 or older, confirmed the benefit of perindopril 8 mg in reducing CV death, MI and cardiac arrest, in patients at lower risk than those studied in HOPE.<sup>7</sup>

The third and final study in this trilogy, the PEACE study, was published in late 2004.<sup>8</sup> PEACE was funded by the U.S. National Institutes of Health, and was initially designed to test the effect of trandolapril 4 mg on CV death and MI in 14,100 patients aged 50 or older with CAD and preserved LV function. As such, PEACE would have been the largest of the three trials. Trandolapril was chosen based upon the impressive reduction in total mortality noted with this once-daily agent in the TRACE study in subjects with LV dysfunction. However, part way through the PEACE trial in 1997, and prior to the publication of HOPE and EUROPA, it became apparent that the goal of 14,100 patients could not be achieved with available funding. The sample size was significantly

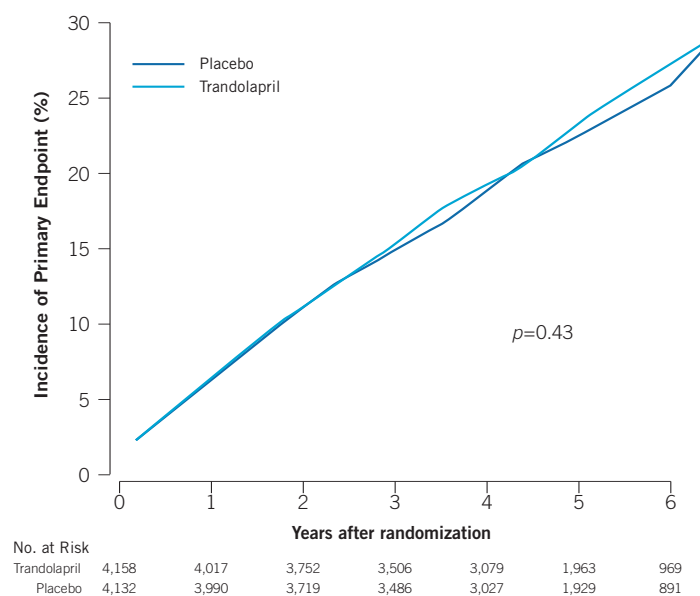


Figure 1. Cumulative incidence of the primary endpoint, according to treatment group

reduced to 8,100 patients, requiring additional events to maintain adequate statistical power. Therefore, the primary endpoint in PEACE was expanded to include the need for revascularization, in addition to CV death and MI.

A total of 8,290 patients were randomized between 1996 and 2000, with a median follow-up of 4.8 years. Baseline characteristics were well matched between the treatment and placebo groups, and vital status at the end of the study was known in 99.5% of subjects (see Table 1). The mean ejection fraction was essentially normal (58%), and patients were on high levels of background therapy, including anti-platelet agents, beta-blockers, and statins. In addition, more than 70% of subjects had been revascularized prior to study enrolment. Approximately 75% of subjects assigned to trandolapril remained on study drug at 3 years, and approximately 8% of placebo patients started taking open-label ACE inhibitors during this time. The target dose of 4 mg of trandolapril was achieved in 69% of patients at 3 years. Compared to placebo, trandolapril resulted in a 3/1 mm Hg reduction in blood pressure at 3 years. Both treatments were well tolerated, with a significant (and expected) increase in the incidence of cough and syncope associated with trandolapril.

No difference was observed between trandolapril and placebo in the primary endpoint of CV death, MI and revascularization ( $p=0.43$ ) (see Figure 1). Approximately 22% of patients in each group experienced one of the primary endpoints, with revascularization accounting for the vast majority of endpoints (>80%). Pre-specified subgroup analyses did not reveal any subgroup that seemed to benefit from treatment with trandolapril.

Secondary endpoints deserve consideration in PEACE. A 24% reduction in the risk of stroke was observed, with a strong trend towards significance ( $p=0.09$ ). Trandolapril was also associated with a significant 25% reduction in heart failure hospitalization and death ( $p=0.02$ ) (see Table 2), and with a 17% reduction in new-onset diabetes ( $p=0.01$ ). There was an 11% relative risk reduction in all-cause mortality associated with trandolapril, which is consistent with other trials of ACE inhibition (HOPE and EUROPA), although this did not reach statistical significance ( $p=0.13$ ). Table 3 shows a meta-analysis of the HOPE, EUROPA and PEACE data, demonstrating the consistency in mortality reductions seen in these trials.<sup>9</sup>

In their conclusions, the authors suggest that PEACE patients were inherently at low risk for CV events, given their baseline characteristics and intensive background evidence-based therapy, including anti-platelet agents, statins, beta-blockers, and revascularization. In such well-treated patients, they argue, whose annualized mortality rates were similar to the U.S. general population, the addition of an ACE inhibitor does not confer any additional benefit. ▶

**Table 1. Baseline characteristics of patients in PEACE\***

Characteristic	Trandolapril (N=4,158)	Placebo (N=4,132)
Age (yr)	64±8	64±8
Age > 75 yr (% of patients)	11	11
Female sex (% of patients)	19 <sup>†</sup>	17
White race (% of patients) <sup>‡</sup>	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 <sup>†</sup>	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 <sup>†</sup>	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 (%) <sup>§</sup>	58±10	58±9
Ejection fraction > 40% and < 50% (% of patients) <sup>¶</sup>	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.

<sup>†</sup> P < 0.05 for the comparison with placebo.

<sup>‡</sup> Race was self-declared.

<sup>§</sup> Data on ejection fraction were available for 3,952 patients in the trandolapril group and 3,926 patients in the placebo group.

<sup>¶</sup> Four patients had ejection fractions between 30 percent and 50 percent.

**Despite the neutral effects on the primary endpoint, consistent benefits with trandolapril were observed on important secondary endpoints, including stroke, heart failure, and prevention of diabetes.**

How then does the clinician resolve the discrepant findings of the PEACE study with the earlier results from HOPE and EUROPA? Should ACE inhibitors be withheld from apparently low-risk patients with CAD and preserved LV function? The answer lies in a careful analysis and comparison of the design and findings of the three trials.

HOPE (9,297 patients) and EUROPA (12,218 patients) were both designed to evaluate ACE inhibitor effects on hard outcomes: CV death, MI and stroke in HOPE, and CV death, MI and cardiac arrest in EUROPA. These endpoints are largely independent of physician attitudes or practice patterns. In PEACE, the addition of revascularization significantly weakened the study. Firstly, the decision to revascularize a patient is often influenced by physician and patient attitudes, more so than by a pharmacological agent. Secondly, previous studies of ACE inhibition, including HOPE and EUROPA, have demonstrated a modest effect, at best, of ACE inhibitors on reducing the need for revascularization. In the HOPE study, although the 15% benefit on revascularization was statistically significant, the benefit of ramipril on hard endpoints, such as MI and mortality, was much greater. In EUROPA, there was no benefit whatsoever of perindopril on revascularization rates. Thus, in order for PEACE to adequately test the benefits of trandolapril on hard endpoints, a larger sample size (as had been originally planned) was clearly necessary.

In comparing background therapy across the three trials, several points are important to consider. The HOPE study began in

1994, at a time when even lipid-lowering therapy was considered controversial in such patients. As well, at least 20% of HOPE participants did not have CAD, as the inclusion criteria included diabetics and those with peripheral arterial disease and cerebrovascular disease. In many of these subjects, at that time, there was no indication for the use of other drugs, such as anti-platelet agents or beta-blockers. By the end of the HOPE study, almost 50% of subjects were receiving lipid-lowering therapy. In addition, further analyses of the HOPE data revealed that there was consistent benefit of ramipril, regardless of whether patients were taking other evidence-based drugs. EUROPA patients were more similar to PEACE patients, with minimal differences in background therapy, and only slightly higher event rates than PEACE patients. Total mortality was actually similar in both EUROPA and PEACE. Despite the similarity in these two patient populations, EUROPA demonstrated a highly significant 20% reduction in its primary endpoint, whereas PEACE did not. HOPE achieved a 22% relative risk reduction and, in fact, a statistically significant reduction was noted in each component of the primary endpoint. Therefore, the neutral results of PEACE cannot be ascribed to either better background therapy or to a lower-risk population.

Had PEACE been the only trial to address the role of ACE inhibition in subjects with CAD and preserved LV function, perhaps it would be reasonable to curtail use of these drugs in such patients. However, as with all evidence-based treatments, clinical decisions must be made after consideration of an entire body of evidence. ■

Although there has been a large statin trial that failed to show benefit, we continue to use this class of drugs based on the findings of numerous other studies. In the case of ACE inhibitors, several large and independent trials in heart failure clearly showed a reduction in MI in the 1990s, a finding that was subsequently confirmed in HOPE and EUROPA. Despite the neutral effects on the primary endpoint, consistent benefits with trandolapril were observed on important secondary endpoints, including stroke, heart failure, and prevention of diabetes.

In summary, the PEACE study was initially well designed and poised to confirm the findings of the earlier HOPE and EUROPA studies. However, the reduction in sample

size, and inclusion of revascularization in the primary endpoint, markedly weakened the power of PEACE to assess the effects of trandolapril on hard CV endpoints. By incorporating the results of PEACE alongside the impressive body of evidence with ACE inhibition, the informed clinician will continue to use ACE inhibitors in the vast majority of patients with cardiovascular disease. ■



EXPERT OPINIONS: CLINICAL IMPACT

**Table 2. Post-hoc analyses of secondary endpoints and other outcomes**

Outcome	Trandolapril (n=4,158)	Placebo (n=4,132)	Hazard ratio (95% CI)	P value
CHF				
As primary cause of hospitalization or death	2.8%	3.7%	0.75 (0.59-0.95)	0.02
As primary cause of hospitalization	2.5%	3.2%	0.77 (0.60-1.00)	0.05
As primary cause of death	0.4%	0.6%	0.59 (0.31-1.13)	0.11
Stroke	1.7%	2.2%	0.76 (0.56-1.04)	0.09
Onset of new diabetes*	9.8%	11.5%	0.83 (0.72-0.96)	0.01

\* The analysis included 3,432 patients in the trandolapril group and 3,472 patients in the placebo group and excluded patients with diabetes at baseline.

**Table 3. Meta-analysis of data on mortality from the HOPE, EUROPA and PEACE trials<sup>6-9</sup>**

Trial	ACE inhibitor No. of deaths/No. of patients (%)	Control No. of deaths/No. of patients (%)	Odds ratio (95% CI)	P value
HOPE	482/4,645 (10.4)	569/4,652 (12.2)	0.83 (0.73-0.95)	0.005
EUROPA	375/6,110 (6.1)	420/6,108 (6.9)	0.89 (0.77-1.02)	0.098
PEACE	299/4,158 (7.2)	334/4,132 (8.1)	0.88 (0.75-1.04)	0.126
<b>Total</b>	<b>1,156/14,913 (7.8)</b>	<b>1,323/14,892 (8.9)</b>	<b>0.86 (0.79-0.94)</b>	<b>&lt; 0.001</b>

## references

1. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;327:669-77.
2. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
3. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685-91.
4. The AIRE Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The acute infarction ramipril efficacy (AIRE) study investigators. *Lancet* 1993;342:821-8.
5. Køber L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;333:1670-6.
6. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342:145-53.
7. The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;362:782-88.
8. The PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;351:2058-68.
9. Yusuf S, Pogue J. ACE inhibition in stable coronary artery disease. *N Engl J Med* 2005;352:937-8.

EXPERT OPINIONS: CLINICAL IMPACT is published by E.O.C.I. Pharmacomm Ltd. 4020 Saint-Ambroise Street Suite 495 Montréal, QC H4C 2C7 Telephone: 514.935.1840 Fax: 514.221.3100. info@ocipharma.com No part of this newsletter may be reproduced, in whole or in part, without the written permission of the publishers. Views expressed are those of the participants and do not necessarily reflect those of the publisher or the sponsor. Support for distribution of this report was provided by Abbott Laboratories, Limited and Fournier Pharma Inc. through an unrestricted grant. Any therapies mentioned in this report should be used in accordance with the recognized prescribing information in Canada. No claims or endorsements are made for any products, uses or doses presently under investigation. E.O.C.I. Pharmacomm Ltd. does not assume liability for content. All rights reserved. Copyright ©2004. Publications Mail Agreement Number: 40816046

The editor wishes to acknowledge the major commitment to unbiased continuing education within the cardiovascular community demonstrated by Abbott Laboratories, Limited and Fournier Pharma Inc., whose financial contribution in the form of an unrestricted educational grant makes the publication of Expert Opinions possible.

