

PEACE – an important yet neutral study of low-risk patients with CAD

The PEACE trial, which was designed to assess the value of ACE inhibition therapy in addition to intensive modern therapy in patients with CAD and normal left ventricular function, has not shown additional benefit from ACE inhibition therapy in this low-risk patient group. Trandolapril therapy was, however, associated with effective blood pressure lowering and a reduction in new-onset diabetes.

Announcing the results of the PEACE (Prevention of Events with Angiotension Converting Enzyme inhibition) study at the recent American Heart meeting in New Orleans, the co-chairman, Prof M.A. Pfeffer of Harvard Medical School emphasised that while prior studies such as HOPE (Heart Outcomes Prevention Evaluation) and EUROPA (EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease) had recruited similar patients, these patients had a higher risk of adverse cardiovascular events than patients in the PEACE trial.

The PEACE trial was a double-blind, placebo-controlled study in which 8 290 patients were randomly assigned to receive either trandolapril at a target dose of 4 mg per day (4 158 patients) or matching placebo (4 132 patients).

The mean (\pm S.D.) age of the patients was 64 ± 8 years, mean blood pressure was $133 \pm 17/78 \pm 10$ mmHg, and the mean left ventricular ejection fraction was $58 \pm 9\%$. The patients received intensive treatment, with 72% having previously undergone coronary revascularisation and 70% receiving lipid-lowering drugs. The incidence

of the primary end point – death from cardiovascular causes, myocardial infarction, or coronary revascularisation – was 21.9% in the trandolapril group, compared with 22.5% in the placebo group (hazard ratio in the trandolapril group 0.96; 95% confidence interval, 0.88 to 1.06; $p = 0.43$) over a median follow-up period of 4.8 years.

Contrasting HOPE, EUROPA and PEACE

The reasons for the lack of clear benefit in this trial are being debated and will continue to be discussed in the months ahead. Two of the South African experts attending the American Heart meeting present their views in an interview with the *Cardiovasc J South Afr* news team (see below).

The major factors considered to play a role are: improved serum lipid levels, a preserved left ventricular ejection fraction of 58%, normal creatinine levels, an average blood pressure at baseline, which was achieved with the use of ACE inhibition in both HOPE and EUROPA, and improved coronary revascularisation before enrollment.

The advent of left ventricular systolic dysfunction results in or provides the stimulus for the activation of various neurohormones, cytokines, growth factors and signaling pathways. It has been suggested that patients with left ventricular systolic dysfunction may require higher doses of an ACE inhibitor, as was utilised in both HOPE and EUROPA.¹

Role of trandolapril in PEACE

Of particular interest in PEACE was that randomisation to trandolapril was associated with a clear and sustained reduction of 4.5 mmHg in systolic pressure, compared with randomisation with a placebo, in which a reduction of 1.5 mmHg was observed. It was also associated, in a *post hoc* analysis, with reductions in the number of patients in whom diabetes developed and the number who required hospitalisation for the management of heart failure, as has been observed with other ACE inhibitors.²

These findings provide strong evidence of the pharmacological activity of the standard dose of trandolapril (4 mg per day).

Dr Mark Pfeffer, co-chairman of the PEACE study, commented that in terms of other outcomes of interest; there were fewer heart failure events, such as hospitalisation for heart failure, in the trandolapril group. 'Of the 6 900 patients who entered the trial without a history of diabetes, the clinical development of diabetes was more likely in those who were not randomised to trandolapril.'

According to Dr Pfeffer, PEACE was clearly a lower-risk group. 'The best way to look at global risk is to look at event rates. The PEACE

Prof Lionel Opie, Director of the Hatter Institute for Cardiovascular Research, University of Cape Town.



Click here for Prof Opie's comments.

Dr Eric Klug, cardiologist, Sunninghill and Sunward Park Hospitals.



Click here for Dr Klug's comments.

TABLE I. SOME BASELINE RISK CHARACTERISTICS OF PATIENT COHORTS IN THE THREE STUDIES USING ACE-INHIBITORS IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE.

	HOPE	EUROPA	PEACE
Lipid levels at baseline (mmol/l)	–	>6.5*	5
Left ventricular ejection fraction (%)	Not measured in all patients	Not assessed	58 \pm 9
Blood pressure at baseline (mmHg)	139/79	137/82	133/78
Coronary revascularisation before enrollment (%)	40	54	72

*All on lipid-lowering treatment.

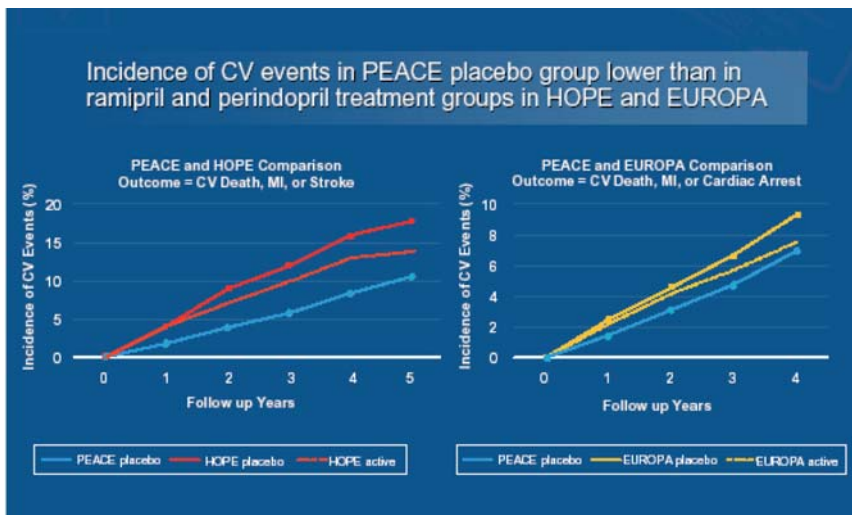


Fig. 1. Comparison of outcomes in the PEACE, HOPE and EUROPA trials.

placebo patients were less at risk than the HOPE placebo patients, and even less at risk than those patients in the HOPE active treatment arm. The PEACE placebo patients were also less at risk than the ACE-treated patients, in the EUROPA study.'

'Looking at causes of death, in HOPE 63% of deaths were cardiovascular in cause, compared with 59% in EUROPA and 47% in PEACE. Annualised CV mortality rate was 1.62 for HOPE, 0.97 for EUROPA and 0.77 for PEACE. Moreover, if we annualise all-cause mortality in the PEACE population, it is 1.6% per year, which is equivalent to the age and gender-matched general population.'

1. Pitt B. ACE inhibitors for patients with vascular disease without left ventricular dysfunction – may they rest in PEACE? *N Engl J Med* 2004; **351**(20): 2115–2117.
2. Braunwald MD for PEACE Investigators. Angiotension-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004; **351**: 2058–2068.

Interview with South African experts

Prof Lionel Opie, Director of the Hatter Institute for Cardiovascular Research, University of Cape Town.

'While accepting the rationale that the much lower risk profile of patients in the PEACE trial influenced the outcome to a zero effect, we need also to look at evidence-based differences within the class of ACE-inhibitors.

'In the ALLHAT study of hypertensive patients with a high risk of cardiovascular events, the use of water-soluble lisinopril did not offer additional benefit in cardiovascular outcomes over the diuretic, chlorthalidone. The PEACE trial has, in lower-risk patients who were mostly revascularised, not shown further benefit in lowering primary end-points with the addition of trandolapril (4 mg), while the HOPE trial (ramipril – 10 mg given at night) and the EUROPA trial (perindopril – 8 mg) did show benefit in their selected cohort of patients.'

'The clinicians will need to weigh the overall evidence and the risk factors in their treatment of patients at risk of further coronary events.'

Dr Eric Klug: Private practice cardiologist, Sunninghill Hospital and Sunward Park Hospital, Johannesburg. Dr Klug also runs a heart failure clinic at the Johannesburg Hospital and has a special interest in heart failure.

Q: Did PEACE show a clear benefit?

A: No it did not, it was what I would call a neutral study. However, this is a very important study, with many lessons for us. The key is that we cannot extrapolate findings from studies such as HOPE and EUROPA to support giving all vascular patients an ACE inhibitor.

PEACE clearly showed that if you

have a well-treated group of ischaemic patients, who have been revascularised and are on almost optimal secondary preventive therapy, any remaining risk is so low that the law of diminishing returns is at work – the remaining risk was so low that the trial was neutral. This was not because ACE inhibitors do not work, but because the study population had such a low baseline risk.

Consequently, if you have a patient who has been revascularised, has preserved LV function, and is on secondary preventive therapy including aspirin, probably a beta-blocker and lipid-lowering therapy, then an ACE inhibitor is not required unless indicated for other reasons. That is the biggest lesson from this study.

Q: How would you put the three trials HOPE, EUROPA and PEACE into context?

A: HOPE was the highest-risk patient population, EUROPA a lower-risk population, and PEACE the lowest-risk population of the three. For example the annualised placebo group mortality rate was 4% in HOPE, and in PEACE it was 1.6%. You are therefore dealing with a much lower risk group in PEACE, who have a lower entry blood pressure, and have been revascularised.

Furthermore, in HOPE only 29% of patients were on lipid-lowering therapy, compared with 70% in PEACE. Aspirin was used in only 76% of the HOPE population, compared with 90% of patients in PEACE.

The annualised mortality in PEACE is almost that of the normal age-matched population. It would be very difficult to find a benefit for a drug in this population.

Treatment with trandolapril, however, was not without benefit. Blood pressure and newly emergent diabetes were reduced, as were hospitalisations for heart failure.

Q: What role, if any, did the increased use of statins in PEACE over EUROPA and HOPE play in the results?

A: This may be important because both drugs may be targeting the same path-

way of inflammation and atherosclerosis. If you have 70% of patients on lipid-lowering therapy in PEACE, and only 56% in EUROPA, that is clearly a difference. I think it played a role.

The event rate of the treated arms in EUROPA and HOPE was still higher than the event rate in the placebo arm of PEACE, so they clearly identified a very low risk group in PEACE. It is not apparent whether this low risk was due to lipid-lowering therapy, or to the fact that the majority of patients (72%) in PEACE had been revascularised, compared with only 40% in HOPE and 54% in EUROPA.

In PEACE the majority of patients had been revascularised, had preserved left ventricles, an entry cholesterol of 5 mmol/l, a systolic blood pressure below 135 mmHg, and were on statin therapy. To find an additional benefit of a further drug on top of all that would be very difficult.

Q: Are there implications for clinical practice?

A: Yes, I think this is a very important study. Several opinion leaders have advocated 'ACE inhibitors for everybody' – the 'polypill' for all vascular

patients. This study clearly shows that an ACE inhibitor is not required if patients fit the recruitment criteria for the PEACE trial – which, in practice, is many patients. These are patients with a preserved left ventricle, and revascularised patients who are stable. It is the law of diminishing returns.

I found this a very useful and practical study. The question we face as clinicians is: do you add an ACE inhibitor to all patients with vascular disease – if they are in this low-risk category? The answer is clearly no.