

Trandolapril did not reduce cardiovascular death or other events in stable coronary artery disease

Braunwald E, Domanski MJ, Fowler SE, *et al.* Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;**351**:2058–68.










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Internal medicine ★★★★★☆☆ Cardiology ★★★★★☆☆



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Q In patients with stable coronary artery disease (CAD) and preserved left ventricular (LV) function, is trandolapril better than placebo for reducing the risk of cardiovascular (CV) death or other CV events?

METHODS

-  **Design:** randomised placebo controlled trial (Prevention of Events with Angiotensin Converting Enzyme Inhibition [PEACE] trial).
-  **Allocation:** concealed.*
-  **Blinding:** blinded (clinicians, patients, {data collectors, and outcome assessors}†).*
-  **Follow up period:** median 4.8 years.
-  **Setting:** 187 centres in the US, Canada, and Italy.
-  **Patients:** 8290 patients (mean age 64 y, 82% men) who had documented CAD (≥ 1 of myocardial infarction [MI], coronary artery bypass grafting [CABG] or percutaneous coronary intervention [PCI] ≥ 3 months before enrolment; or obstruction of $\geq 50\%$ of the luminal diameter of ≥ 1 native vessel or coronary angiography); LV ejection fraction $>40\%$ on ventriculography or echocardiography, a qualitatively normal left ventriculogram, or the absence of LV wall motion abnormalities on echocardiography; tolerance and $\geq 80\%$ compliance with the medication; and successful completion of the run in phase. Exclusion criteria included current use or contraindication of angiotensin converting enzyme (ACE) inhibitors, current use of angiotensin II receptor antagonists, hospital admission for unstable angina within the previous 2 months, valvular heart disease requiring surgical intervention, and CABG or PCI within the previous 3 months.
-  **Intervention:** trandolapril (2 mg/d increased to 4 mg/d after 6 mo, if tolerated) (n = 4158) or matching placebo (n = 4132).
-  **Outcomes:** composite endpoint of death from CV causes, non-fatal MI, and coronary revascularisation (CABG or PCI). Secondary outcomes included death from CV causes, non-fatal MI, and adverse effects.
-  **Patient follow up:** 98% (intention to treat analysis).

*See glossary.
†Information provided by author.

MAIN RESULTS

The trandolapril and placebo groups did not differ for the primary outcome (see table at www.evidence-basedmedicine.com). The groups did not differ for any of the secondary outcomes (hazard ratio range 0.95 to 0.98, 95% lower CI range 0.83 to 0.90, upper CI range 1.03 to 1.12). More patients who received trandolapril

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discontinued the study because of adverse effects than did those who received placebo (14.4% v 6.5%, $p < 0.001$). Adverse effects included cough (39.1% v 27.5%, $p < 0.01$) and syncope (4.8% v 3.9%, $p = 0.04$).

CONCLUSION

In patients with stable coronary artery disease and preserved left ventricular function, trandolapril was not better than placebo for reducing cardiovascular (CV) death or other CV events.

Abstract and commentary also appear in ACP Journal Club.

Commentary

The PEACE trial, the latest in a trifecta of trials evaluating ACE inhibitors for patients who have CV disease without heart failure, did not show a benefit of trandolapril in patients with CAD at low risk of complications. These results were surprising in light of the other trials, and the qualitatively different findings provide important information to clinicians. Possible explanations for the difference include the drug (including dose and compliance), the patient population, and chance. The authors carefully considered these possibilities and showed that compliance was only slightly lower than in other trials and that the drug and its dose (shown to be effective in the TRACE trial¹) had a clear biological effect in PEACE.

Although the trial was well powered to detect a clinically important treatment effect for the primary endpoint, the results included the possibility of up to a 17% relative risk reduction in the harder endpoints of CV death or non-fatal MI. The lack of significant difference may be because revascularisation (especially with PCI) is not a sensitive enough endpoint to detect clinically important benefits in low risk patients. The authors showed that the patients in PEACE had lower risk than those in HOPE, with only about half the annual event rate. This might be explained by the high rates of previous revascularisation, use of statins, somewhat lower blood pressure, and less diabetes. Clinicians should recognise that some of their patients will be at higher risk than those enrolled in the PEACE trial and should not extrapolate the results of the PEACE trial to high risk patients with CAD.

Of interest, fewer patients on trandolapril developed diabetes during the course of the trial, adding support to the intriguing effect of ACE inhibitors and angiotensin receptor blockers for preventing diabetes.

How should PEACE change practice? Low risk patients with revascularised CAD, controlled blood pressure, and without complicated diabetes need not routinely be prescribed ACE inhibitors. However, in light of the overall evidence (including the HOPE and EUROPA trials^{2,3}), high risk patients should receive ACE inhibitors at doses shown to be effective in large clinical trials.

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1 Køber L, Torp-Pedersen C, Carlsen JE, *et al.* *N Engl J Med* 1995;**333**:1670–6.

2 Yusuf S, Sleight P, Pogue J, *et al.* *N Engl J Med* 2000;**342**:145–53.

3 Fox KM; EUROpean trial *Lancet* 2003;**362**:782–8.