Perindopril reduced cardiac events in stable coronary artery disease

Fox KM. **Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study).** Lancet. 2003;362:782-8.

QUESTION

In patients with stable coronary artery disease (CAD), does the angiotensin-converting enzyme (ACE) inhibitor perindopril reduce cardiac events?

DESIGN

Randomized {allocation concealed*}†, blinded (patients, clinicians, {data collectors, and outcome assessors}†),* placebo-controlled trial with mean 4.2-year follow-up (EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease [EUROPA]).

SETTING

{424 centers in 24 countries}‡.

PATIENTS

Patients ≥ 18 years of age who had CAD but no evidence of heart failure were eligible. CAD was defined as myocardial infarction (MI) > 3 months before screening, coronary revascularization > 6 months before screening, or angiographic evidence of ≥ 70% narrowing of ≥ 1 major coronary artery, or men with chest pain and a positive cardiovascular stress test result. Exclusion criteria included planned revascularization, hypotension, uncontrolled hypertension, recent use of ACE inhibitors or angiotensin-receptor blockers, renal insufficiency, and serum potassium level > 5.5 mmol/L. 12 218 patients (mean age 60 y, 85% men) completed a 4-week run-in period and were randomized; follow-up was > 99%.

INTERVENTION

Patients were allocated to perindopril, 8 mg/d (n = 6110), or placebo (n = 6108) for ≥ 3 years.

MAIN OUTCOME MEASURES

Composite endpoint of cardiovascular mortality, nonfatal MI, and nonfatal cardiac arrest. Secondary outcomes were a composite of total mortality, nonfatal MI, hospital admission for unstable angina, and resuscitated cardiac arrest; and individual components of the composite.

MAIN RESULTS

Analysis was by intention to treat. Fewer patients who received perindopril reached the primary composite endpoint than did patients who received placebo (Table). Also, fewer perindopril recipients reached the secondary composite endpoint (Table). When the secondary outcomes were taken individually, perindopril reduced fatal and nonfatal MI and hospital admission for heart failure.

CONCLUSION

In patients with stable coronary artery disease, perindopril reduced cardiovascular mortality, nonfatal myocardial infarction, and resuscitated cardiac arrest.

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*See Glossary.

†Information provided by author.

‡**Gomma AH, Fox KM.** Cardiovasc Drugs Ther. 2001;15:169-79.

Perindopril vs placebo for stable coronary artery disease at mean 4.2 years§

Outcomes	Perindopril	Placebo	RRR (95% CI)	NNT (CI)
Primary composite endpoint	8.0%	9.9%	20% (9 to 29)	54 (35 to 115)
Secondary composite endpoint	14.8%	17.1%	14% (6 to 21)	44 (28 to 102)

§Primary composite endpoint was cardiovascular mortality, nonfatal myocardial infarction, and resuscitated cardiac arrest; secondary composite endpoint was total mortality, nonfatal myocardial infarction, unstable angina, and resuscitated cardiac arrest. Abbreviations defined in Glossary; NNT and CI calculated from data in article.

COMMENTARY

The HOPE study (1) supported the widespread use of the ACE inhibitor ramipril to prevent cardiovascular events. However, several questions remained and many physicians had reservations about changing practice based on a single, albeit large and well-designed, study. Furthermore, the patient population in HOPE included many diabetic patients with hypertension and kidney disease, a group many believe already required long-term ACE inhibitor therapy, which may have driven the results of the overall trial.

By design, the EUROPA study had fewer diabetic patients than HOPE, but all patients had CAD. EUROPA required a run-in phase and then withdrew the drug in the placebo group so that all patients intolerant of ACE inhibitors were eliminated from both study groups. Also in EUROPA, fewer patients had peripheral vascular disease and hypertension, they were younger, and they were more frequently treated with HMG-CoA reductase inhibitors and platelet inhibitors. Accordingly, the event rate in the placebo group was 40% to 80% lower than that of the placebo group in HOPE. Therefore, concomitant medical therapy was representative of current clinical practice, making it more difficult to detect a treatment benefit from additional therapy.

Nevertheless, in EUROPA, all major adverse cardiovascular events were reduced by perindopril. Since event rates were lower in EUROPA than HOPE, it is not surprising that the absolute reduction in events was less. However, the results of EUROPA are very much in accord with the results of HOPE, and extend the administration of perindopril to a wider population with CAD.

Although these studies show that both perindopril and ramipril reduce cardiovascular events, neither directly supports or addresses whether perindopril, ramipril, and other ACE inhibitors are equally efficacious. Perindopril and ramipril are highly tissue-specific ACE inhibitors. As tissue ACE may be the primary target of therapy, the specificity of tissue ACE inhibition may be important. Therefore, we cannot generalize with certainty the results of EUROPA and HOPE to less tissue-specific ACE inhibitors. Even clinicians who believe that the benefits of ACE inhibitors are a class effect and not unique to tissue-specific ACE inhibitors acknowledge that the right dose and dosing strategy must be identified for each indication before it is assumed that all ACE inhibitors are equal.

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Reference

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