ACE inhibition in stable coronary artery disease

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: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;362:782-88.

Background: Effective secondary prevention strategies for patients with chronic coronary artery disease (CAD) are important for several reasons: (a) the size of this population is enormous and growing every year, particularly owing to continuing increases in life expectancy and decreases in rates of death from acute myocardial infarction; (b) the risk of morbidity and death remains high despite risk-factor modification and treatment with ASA, statins and β blockers; and (c) CAD is the leading cause of death and contributor to health care costs in many regions of the world.[1]

Question: Does treatment with the angiotensin-converting-enzyme (ACE) inhibitor perindopril reduce cardiovascular risk in a relatively low-risk population with stable CAD and no apparent heart failure?

Design: In this randomized, double-blind, placebo-controlled study, patients with documented evidence of CAD were enrolled if there was no evidence of heart failure, planned revascularization, hypotension, uncontrolled hypertension, renal insufficiency or hyperkalemia. After a 4-week run-in period, during which all patients received perindopril, 12 218 patients were randomly assigned to receive either 8 mg of perindopril once daily or matching placebo for a mean follow-up of 4.2 years. The primary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction and cardiac arrest. Analysis was by intention to treat.

Results: Key baseline characteristics of the patients are shown in Table 1. Loss to follow-up was 0.02%. In all, 10% of the patients given placebo and 8% of those given perindopril experienced the primary end point, for a relative risk reduction [RRR] of 20% (95% confidence interval [CI] 9%–29%; p = 0.0003). The benefit began to appear at 1 year and increased through the course of the trial. The effect of perindopril was consistent across predefined subgroups. Compared with placebo, perindopril was associated with significant reductions in several secondary end points, in particular hospital admission because of heart failure (RRR 39%, 95% CI 17%–56%; p = 0.002) and fatal and nonfatal myocardial infarction (RRR 24%; $p < 0.001$).

Commentary: The EUROPA study extends previous findings from the landmark Heart Outcomes Prevention Evaluation (HOPE) trial to a substantially lower risk group of patients with stable chronic CAD.[2] Key differences between the 2 trials include a much higher incidence of diabetes, peripheral vascular disease and cerebrovascular disease in the HOPE trial and a significantly higher frequency of treatment with antiplatelets, statins and β blockers in the EUROPA trial. Despite these differences, the reductions in major cardiovascular events were largely similar across the 2 trials (e.g., 24% reduction in myocardial infarction in EUROPA v. 20% in HOPE).[2] The benefits reported for perindopril in the EUROPA trial appeared to accrue on top of standard preventive therapies (e.g., antiplatelets and β blockers) and were evident regardless of the presence or absence of such risk factors as previous myocardial infarction, hypertension or diabetes.

Practice implications: Seemingly low-risk patients with CAD, such as those with a remote history of myocardial infarction who are otherwise asymptomatic and others with mild stable angina, will benefit from the addition of an ACE inhibitor to an optimal therapeutic regimen consisting of an antiplatelet, β blocker and cholesterol-lowering drug. Selection of a tissue-active ACE inhibitor with a long half-life that has been validated in a large clinical trial (e.g., ramipril or perindopril) is preferable, with every attempt made to match the dose shown to be effective in the trial. After allowing for noncompliance in the EUROPA trial, 1 cardiovascular death or myocardial infarction would be prevented for every 36 patients treated for 4 years with perindopril.[3]

Table 1: Selected baseline characteristics of patients in the EUROPA trial

Characteristic	Group; % of patients*	
	Perindopril	Placebo
Mean age (and SD), yr	60 (9)	60 (9)
Female sex	14.5	14.7
History of myocardial infarction	64.9	64.7
Cerebrovascular disease	3.4	3.3
Hypertension	27.0	27.2
Diabetes mellitus	11.8	12.8
Medications		
Antiplatelets	91.9	92.7
Lipid-lowering drugs	57.8	57.3
β Blockers	62.0	61.3

Note: SD = standard deviation.
*Unless stated otherwise.

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References

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