

THERAPEUTICS

Ramipril reduced mortality and cardiovascular morbidity in high-risk adults

The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on death from cardiovascular causes, myocardial infarction, and stroke in high-risk patients. *N Engl J Med.* 2000 Jan 20;342:145-53.

QUESTION

In adults who are at high risk for cardiovascular (CV) events, does ramipril, an angiotensin-converting enzyme (ACE) inhibitor, reduce CV events? (Vitamin E results will be reported separately.)

DESIGN

Randomized {allocation concealed*}†, blinded (patients, clinicians, and outcome assessors),* controlled 2 × 2 factorial design trial with planned interim analyses (Heart Outcomes Prevention Evaluation [HOPE] study).

SETTING

161 centers in North America, 76 in 14 western European countries, and 30 in Argentina and Brazil.

PARTICIPANTS

9541 adults (mean age 66 y, 73% men) who were age ≥ 55 years and had a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes and ≥ 1 other CV risk factor. Exclusion criteria were heart failure, ejection fraction < 0.4, use of an ACE inhibitor, uncontrolled hypertension, nephropathy, or myocardial infarction (MI) or stroke. Follow-up was > 99.9%.

INTERVENTION

Adults were allocated to ramipril, 2.5 mg/d for 1 week, 5 mg/d for 3 weeks, then 10 mg/d (n = 4645), or to placebo (n = 4652).

MAIN OUTCOME MEASURES

MI, stroke, and CV mortality.

MAIN RESULTS

The study was stopped early. Adults in the ramipril group had lower rates of combined MI, stroke, or CV mortality; MI; stroke; CV mortality; all-cause mortality (P for all comparisons ≤ 0.006) (Table); revascularization procedures (16% vs 18%, P < 0.002); cardiac arrest (0.8% vs 1.3%, P = 0.02); heart failure (9% vs 12%, P < 0.001); and complications related to diabetes (6% vs 8%, P = 0.03) than did adults in the placebo group.

CONCLUSION

Ramipril reduced mortality and cardiovascular morbidity in adults at high risk for cardiovascular events.

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*See Glossary.

†The HOPE Study Investigators. *Can J Cardiol.* 1996;12:127-37.

Ramipril vs placebo for adults at high risk for cardiovascular (CV) events†

Outcomes at mean 4 y	Ramipril	Placebo	RRR (95% CI)	NNT (CI)
MI, stroke, or CV mortality	14%	18%	22% (14 to 30)	26 (19 to 43)
CV mortality	6%	8%	26% (13 to 36)	50 (33 to 105)
MI	10%	12%	20% (10 to 30)	42 (27 to 89)
Stroke	3%	5%	32% (16 to 44)	67 (43 to 145)
All-cause mortality	10%	12%	16% (5 to 25)	56 (32 to 195)

†CV = cardiovascular; MI = myocardial infarction. Other abbreviations defined in Glossary; RRR, NNT, and CI provided by authors.

COMMENTARY

Over the past decade, several studies have documented that ACE inhibitors reduce all-cause mortality and probably CV morbidity in patients with left ventricular dysfunction and congestive heart failure. The HOPE study was designed to assess whether ACE inhibitors may also prevent CV events in a broader spectrum of high-risk patients. This hypothesis was convincingly confirmed regardless of left ventricular function. Benefit was found across all subgroups and was additive to other therapies with proven secondary preventive effects. Furthermore, the preventive effect was beyond that expected from blood pressure lowering. The findings strongly support a direct CV protective effect of ramipril.

Of interest, patients with diabetes had the same relative benefit as patients without diabetes, despite the fact that the investigators had not required established CV disease for inclusion of the patients with diabetes. This finding strengthens the hypothesis that patients with diabetes should receive active preventive therapies. In a recent meta-analysis, Golan and colleagues (1) argued that treating all middle-aged patients with type 2 diabetes with ACE inhibitors on the basis of the

protective effects on the kidneys alone would be cost-effective. Considering the HOPE study results, this strategy is even more justified. The 30% reduction in new-onset diabetes is also important but needs to be confirmed. Ramipril was easy to introduce and often well tolerated. Direct treatment costs will certainly increase as ACE inhibitors are used more often. However, the HOPE study may also provide the basis for savings, for example, through fewer echocardiographic screening tests of left ventricular function after MI and fewer revascularizations.

In the light of available evidence, we recommend that all middle-aged patients with either established CV disease or diabetes and 1 additional risk factor (which almost all middle-aged patients with diabetes have) should be considered for treatment with ACE inhibitors.

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Reference

1. Golan L, Birkmeyer JD, Welch HG. *Ann Intern Med.* 1999;131:660-7.