# HOPE study

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**Special Session IV: Clinical Trial Results[1]**

## HOPE (Heart Outcomes Prevention Evaluation) Trial

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## Objective

Randomized trial of the ACE inhibitor ramipril and vitamin E in patients at high risk for cardiovascular events versus
placebo. Primary end point of the study was composite of myocardial infarction, stroke, or death from cardiovascular causes.

## Inclusion Criteria

Patients aged >55 years at high risk for cardiovascular events because of:

any evidence of vascular disease (CHD, stroke, PVD).

diabetes plus 1 other coronary risk factor.

## Exclusion Criteria

Heart failure or low ejection fraction; patient already on ACE inhibitor therapy or vitamin E.

## Study Design

A total of 9297 patients were randomly assigned to receive ramipril (10 mg per day) or placebo for a mean of 5
years. In addition, all patients were randomly assigned to receive vitamin E, 400 IU/day, or placebo.

## Patient Characteristics

Mean age was 66 years, with just over 25% female; 80.6% had any evidence of coronary artery disease, 52.8% a previous MI, 43.4% peripheral vascular disease, 38.3% diabetes, 46.5% hypertension, 65.8% an elevated cholesterol. Antiplatelet therapy (aspirin or other) was being taken by 76% at the time of enrollment, beta-blockers by 40%, and lipid-lowering agents by 28.9%.

## Results

The data safety monitoring board recommended termination of the study in early, March 1999, owing to an overwhelming benefit of ramipril.

Vitamin E vs Placebo: There were no significant differences in the primary outcome of death, MI, stroke (16.2% in vitamin E group vs 15.5% in placebo; P= .35). All-cause mortality was not different between the 2 groups, either.

Ramipril vs Placebo: In the ramipril group, there was a significant reduction in the primary end point from 17.7% in placebo to 14.1% in the treatment group (relative risk reduction of 22%; P = .000002). There was also a significant reduction in MI, stroke, and cardiovascular death. In addition, all-cause mortality was significantly reduced by 16% in the ramipril group (P = .0058).

Kaplan-Meier survival curves separated at 200+ days and continued to diverge. Ramipril also reduced the onset of new congestive heart failure (11.7% in placebo vs 9.2% in ramipril; 23% reduction; P = .00004), and resulted in need for revascularization reduced by 16% (P = .0005). The benefits of ramipril were seen in virtually all pre-specified subgroups -- patients with or without coronary artery disease, diabetics and nondiabetics, young (< 65 years) and old patients, hypertensives and nonhypertensives, and in those with and without cerebrovascular disease, peripheral vascular disease, or microalbuminuria. In addition, renal outcomes were reduced. There was a significant 25% reduction in the development of overt nephropathy from 4% to 3% (P = .010) and a 10% reduction in the development of new microalbuminuria (P = .032). Interestingly, the development of diabetes appears to have been reduced by 32% (P = .002) in the patients taking ramipril. The curves diverged at around 1 year and continued to separate thereafter.

Regarding blood pressure reduction, there was an average reduction in systolic blood pressure of 3.3 mm Hg

in
patients taking ramipril. The benefits on stroke and MI reduction achieved in the HOPE trial (31% and 20%, respectively) appear to be far greater than what would be expected from blood pressure reduction alone. Moreover, the benefits were sustained across various quartiles of systolic and diastolic blood pressure, including
those in the normal range.

## Conclusions

There is overwhelming evidence that, in a broad range of high-risk patients, ramipril prevents
cardiovascular death, stroke, and MI
heart failure, revascularization
development of diabetes
diabetic microvascular complications including nephropathy

The benefits of ramipril are incremental to existing therapy.

The beneficial effects of ramipril are independent of blood pressure lowering.

Vitamin E does not have any significant protective effect.

The only adverse effect to ramipril was a 5% incidence of cough.

Eighteen deaths were prevented for every 1000 patients treated; considering all events (stroke, MI, death, CHF, revascularization, diabetes, diabetic complications, new diabetes, cardiac arrest), a striking 128 events were prevented for every 1000 patients treated, rendering a NNT of 8.

The global impact as summarized by the authors was: if 1/4 of eligible patients in developing countries and 1/2
of those in developed nations were treated, 2 million events would be prevented each year.

## Comment

Beyond a doubt, this is a landmark trial that will change the way we practice medicine. Given these data, the importance of carefully screening patients for risk of cardiovascular events is now vital, as a viable and safe therapeutic agent is now available.

## Reference

1.Grant AO, Luepker R, chairs. Clinical Trial Results. Presented at the American Heart Association 72nd Scientific Sessions, Atlanta, Ga, November 7-10, 1999. Special Session IV, Nov 10.

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