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The HOPE (Heart Outcomes Prevention Evaluation) trial. Overall results and the effect of renal insufficiency on cardiovascular disease

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INTRODUCTION

It has been shown that angiotensin-converting-enzyme inhibitors improve the outcome of patients with left ventricular dysfunction, whether or not they have heart failure. Also, several epidemiologic and experimental studies suggest that the amount of vitamin E ingested in food and in supplements is associated with a lower risk of atherosclerosis and cardiovascular disease. The HOPE trial was initiated to assess the role of an angiotensin-converting-enzyme inhibitor, ramipril, and of vitamin E in patients who were at high risk for cardiovascular events but who did not have left ventricular dysfunction or heart failure.

STUDY METHODS

High-risk patients (55 years of age or older) who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor (hypertension, elevated total cholesterol, low HDL-cholesterol, smoking, microalbuminuria) and who were not known to have a low ejection fraction or heart failure were eligible to participate. They were randomly assigned according to a two-by-two factorial design to receive ramipril (10 mg once per day orally) or matching placebo for a mean of five years (n = 9,297), and to receive either 400 IU of vitamin E daily from natural sources or matching placebo (n = 9,541). The primary outcome was a composite of myocardial infarction, stroke, and death from cardiovascular causes. The secondary outcomes included unstable angina, congestive heart failure, revascularization or amputation, death from any cause, complications of diabetes, and cancer. A total of 3,577 people with diabetes were included in the HOPE trial. Overt nephropathy was also a main outcome in this sub-group.

A post-hoc analysis was performed in 980 patients with mild renal insufficiency (serum creatinine concentration ≥ 124 µmol/l [≥ 1.4 mg/dl]) and 8,307 patients with normal renal function (serum creatinine concentration < 124 µmol/l [< 1.4 mg/dl]) Patients with a baseline serum creatinine concentration greater than 200 µmol/l (2.3 mg/dl) were excluded.

RESULTS

The study was stopped early by the independent data and safety monitoring board because of the obvious benefit of ramipril. Vitamin E treatment had no effect. Median follow-up was 4.5 years. The incidence of stroke was reduced by 32% with ramipril, myocardial infarction by 20% and cardiovascular death by 25%, while there also were significant reductions in the number of revascularization procedures, cardiac arrests, heart failure, and complications related to diabetes. The reduction in the rate of events began within a year after initiation of treatment with ramipril and persisted throughout follow-up. The benefit of the treatment could not be ascribed to the rather small reduction (3/2 mmHg) in blood pressure.

In the diabetic patients ramipril was as effective as in the non-diabetic participants. In addition, it lowered the risk of overt nephropathy by 24%.

The cumulative incidence of the primary outcome was higher in patients with mild renal insufficiency than in those without (22.2% *vs* 15.1%, $p < 0.001$) and increased with serum creatinine concentration. Patients with mild renal insufficiency had a substantially increased risk for cardiovascular death (11.4% *vs* 6.6%) and total mortality (17.8% *vs* 10.6%, both $p < 0.001$). The effect of renal insufficiency on the primary outcome (adjusted hazard ratio, 1.40 [95% CI, 1.16 to 1.69]) was independent of known cardiovascular risks and treatment. Ramipril reduced the

incidence of the primary outcome in patients with and those without renal insufficiency (hazard ratio, 0.80 *vs* 0.79; p > 0.2 for the difference).

CONCLUSIONS

Ramipril significantly reduced the rates of death, myocardial infarction, and stroke in a broad range of high-risk patients. The benefits conferred were in addition to, and largely independent of, other conventional treatments such as aspirin, lipid-lowering agents, beta-blockers, diuretics and calcium channel blockers. The relative risk reduction was very similar whether or not the patient was a known hypertensive at baseline. In patients who had preexisting vascular disease or diabetes combined with an additional cardiovascular risk factor, mild renal insufficiency significantly increased the risk for subsequent cardiovascular events. Ramipril reduced cardiovascular risk in those patients without increasing adverse effects.

Thus, the HOPE trial has directed our attention again to the multifactorial interventions available for reducing cardiovascular complications in patients with diabetes, preexisting cardiovascular disease, and mild renal insufficiency. In addition to strategies to obtain good glycaemic control (in diabetic patients), normal blood pressure, and lipid levels, there is now sufficient evidence that most patients with increased cardiovascular risk will benefit from treatment with the ACE inhibitor ramipril.

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Lancet 2000; 355: 253-259.
Ann Intern Med 2001; 134: 629-636).