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ACE inhibitors and high-risk patients

Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342:145-53.

Background

Angiotensin-converting-enzyme (ACE) inhibitors lower morbidity and mortality among patients with congestive heart failure. In addition to a reduction in afterload, ACE inhibitors have a protective effect on the vasculature, which may lead to a reduction in cardiovascular events in high-risk patients without a history of left ventricular dysfunction.[1]

Question

Do ACE inhibitors lower the incidence of cardiovascular events and death among high-risk patients who do not have a history of congestive heart failure?

Design

A double-blind, multicentre, randomized controlled trial was conducted to compare the effects of ramipril to placebo in 9297 patients over the age of 55 who were at high risk for cardiovascular events. Eligible patients included those with coronary artery disease, stroke, peripheral vascular disease or a history of diabetes mellitus plus another cardiovascular risk factor. Exclusion criteria included congestive heart failure, overt nephropathy or a history of myocardial infarction or stroke within 4 weeks of the study. The primary study outcome was the combination of myocardial infarction, stroke or death from any cardiovascular event.

Results

Almost half of the subjects were older than 65, and just over one-quarter were women. Most patients (80%) had a history of coronary artery disease, about half were hypertensive (46.8%), and many (38.5%) had diabetes mellitus.

A chart audit found that more than half of the patients had had their ventricular function assessed before the study. Of this group, 8.1% had a low ejection fraction without a clinical history of congestive heart failure.

The study was designed to continue for 5 years, but it was stopped early because of the beneficial effects of ramipril on the primary outcome. The primary end point occurred in 14.0% of the patients in the treatment group, as compared with 17.8% in the placebo group.

This result was consistent in both men and women and in all predefined subgroups, including patients with diabetes, hypertension and left ventricular dysfunction. Treatment with ramipril was associated with significant reductions in secondary end points such as cardiac arrest, congestive heart failure, revascularization procedures and death from any cause. The incidence of new diagnoses of diabetes was significantly lower in the ramipril group than in the placebo group (102 v. 155 patients).

Commentary

This large, randomized study documents the beneficial effects of ACE inhibitors in patients at high risk for cardiovascular events. The results were consistent across subgroups, and benefit extended to a number of secondary outcomes. Ramipril was well tolerated, with cough resulting in discontinuation of the medication in 7.3 % of patients.

The intriguing reduction in the incidence of diabetes corresponds to observations in the Captopril Prevention Project study of antihypertensive therapy.[2]

Practice implications

When given ramipril therapy, high-risk patients over age 55 with normal left ventricular function have a reduced rate of myocardial infarction, stroke and death from cardiovascular causes. Ramipril, started at a dose of 2.5 mg/d and titrated over 1 month to a dose of 10 mg/d, is well tolerated. Whether the findings of this study can be extended to angiotensin II receptor inhibitors is unknown.

The reduction in the incidence of diabetes among patients taking the ACE inhibitor is an important observation that merits further investigation. — *Kathryn A. Myers*

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