Angiotensin-converting enzyme inhibitors in coronary artery disease and preserved left ventricular systolic function: a systematic review and meta-analysis of randomized controlled trials

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CRD summary
This review assessed the effects of angiotensin-converting enzyme inhibitors (ACEIs), compared with placebo, in people with coronary heart disease and preserved left ventricular function. The authors concluded that ACEIs have a modest protective effect in reducing death, myocardial infarction, and the need for revascularisation. These conclusions are supported by the data presented.

Authors' objectives
To assess the effects of angiotensin-converting enzyme inhibitors (ACEIs) in people with coronary artery disease (CAD) and preserved left ventricular (LV) function.

Searching
MEDLINE (1966 to February 2005), the Cochrane CENTRAL Register (Issue 1 2005), DARE (Issue 1 2005), EMBASE (1980 to week 6, 2005), BIOSIS Previews (1969 to week 8, 2005) and the U.S. Food and Drug Administration website were searched; the search terms were reported. The reference lists of identified papers and the proceedings from national cardiology scientific sessions of the American Heart Association and the American College of Cardiology (2001 to 2005) were also checked. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with at least 2 years' follow-up were eligible for inclusion.

Specific interventions included in the review
Studies comparing ACEIs with placebo were eligible for inclusion. The included studies assessed ramipril, perindopril, trandolapril, quinapril and enalapril. Some participants were also taking antiplatelets, beta-blockers, lipid-lowering treatment, calcium-channel blockers, or diuretics.

Participants included in the review
Studies on people with CAD and preserved LV function were eligible for inclusion. CAD was defined as prior myocardial infarction (MI), percutaneous or surgical coronary revascularisation, angiographic evidence of atherosclerosis in one or more coronary arteries, or a positive stress electrocardiogram, echocardiogram or nuclear stress test. Preserved LV systolic function was defined as an ejection fraction of at least 40% and/or the absence of congestive heart failure. In the included studies, the mean ages of the participants ranged from 58 to 66 years and 15 to 28% were women. Some participants had diabetes or hypertension. Two studies included a proportion of participants without documented CAD, as they were considered to be of high risk.

Outcomes assessed in the review
To be included, the trials had to report on mortality, nonfatal MI or revascularisation. Changes in systolic and diastolic blood-pressure (SBP and DBP, respectively) and the incidence of newly diagnosed diabetes were also reported.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Quality was assessed on the basis of generation of allocation, allocation concealment, blinding, intention-to-treat analysis and losses to follow-up. The authors did not state how many reviewers performed the quality assessment.

**Data extraction**

One author extracted the data and a second confirmed the extraction. Any discrepancies were resolved by consensus or with a third author. The data were extracted on an intention-to-treat basis. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated for outcomes in the individual studies.

**Methods of synthesis**

**How were the studies combined?**

A random-effects model was used to calculate the pooled RR and 95% CIs. Numbers-needed-to-treat (NNT) to prevent one event were calculated from the pooled absolute risk reduction. Funnel plots were used to assess possible publication bias.

**How were differences between studies investigated?**

Heterogeneity was assessed using the I-squared statistic. Subgroup analyses were performed based on the number of diabetics in the study (less than 20% versus at least 20%) and outcome measures (reduction in SBP, less than 5 mmHg versus at least 5 mmHg; follow-up of at most 2 years versus more than 2 years). Sensitivity analyses examined the effects on the results of the 2 studies that included some people without diagnosed CAD, and of the effect of removing the study contributing the largest number of events to the analyses.

**Results of the review**

Six RCTs (33,500 participants) were included. The mean follow-up ranged from 2 to 4.8 years.

Generation of allocation and allocation concealment were adequate in most studies. All studies were double-blinded, although blinding of the outcome assessment and data analyses was unclear in some studies. All studies used an intention-to-treat analysis.

The percentage of people on the study drug at 3 years ranged from 71 to 81%.

Tests showed no evidence of heterogeneity between the studies and no evidence of publication bias.

ACEI treatment resulted in a mean decrease of 3.9 mmHg in SBP and 1.8 mmHg DBP (5 trials), and a decrease in new onset diabetes (RR 0.76, 95% CI: 0.60, 0.95, p=0.02; 2 trials).

Compared with placebo, ACEI treatment was associated with a reduction in cardiovascular mortality (RR 0.83, 95% CI: 0.72, 0.96, p=0.01), nonfatal MI (RR 0.84, 95% CI: 0.75, 0.94, p=0.003), all-cause mortality (RR 0.87, 95% CI: 0.81, 0.94, p=0.0003) and revascularisation (RR 0.93, 95% CI: 0.87, 1.00, p=0.04). The NNT to prevent one of any of these outcomes was 100.

The results of the sensitivity analyses were similar to those of the main analyses, but with wider CIs. Details were given in the paper.

In subgroup analyses there was no evidence of any significant difference in outcomes between subgroups. Details were given in the paper.

**Authors' conclusions**

ACEI treatment, when added to conventional therapy, has a modest effect in reducing all-cause mortality, cardiovascular mortality, nonfatal MI and revascularisation in people with CAD and preserved LV function.

**CRD commentary**
The aims and inclusion criteria for this review were clearly stated. The search covered several relevant databases and attempts were made to identify unpublished studies and include all studies regardless of language. It is unlikely that relevant studies were missed. The validity assessment was performed using appropriate criteria. While the data were extracted using methods appropriate for minimising bias, the methods used to select studies and assess their quality were not reported.

Appropriate statistical methods were used to analyse and combine the data. Attempts were made to consider the effects of study quality, heterogeneity and publication bias on the findings, although given the small number of included studies these statistical tests were likely to be underpowered. Overall, the authors' conclusions are supported by the data presented.

**Implications of the review for practice and research**

Practice: The authors suggested that evidence supports the use of ACEIs, and that these should be considered in patients with pre-diabetic conditions, hypertension, impaired fasting glucose levels, congestive heart failure or coronary heart disease.

Research: The authors did not state any implications for further research.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.