Tissue ACE inhibitors for secondary prevention of cardiovascular disease in patients with preserved left ventricular function: a pooled meta-analysis of randomized placebo-controlled trials

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CRD summary
The review concluded that tissue angiotensin-converting enzyme inhibitors demonstrated benefit when used for secondary prevention of cardiovascular disease in patients with preserved left ventricular function in randomised placebo-controlled trials. The authors' conclusion represented the evidence presented, but lack of clarity about review methods means that their reliability is unclear.

Authors' objectives
To evaluate the role of tissue angiotensin-converting enzyme inhibitors in secondary prevention of cardiovascular disease in patients with preserved left ventricular function.

Searching
MEDLINE (1996 to 2005), Cochrane Central Register of Controlled Clinical Trials (CENTRAL), and Cochrane Database of Systematic Reviews were searched for English and non-English peer-reviewed published articles. Search terms were reported.

Study selection
Eligible for inclusion in the review were randomised placebo-controlled trials with a mean duration of at least 12 months of tissue selective angiotensin-converting enzyme inhibitors (ramipril, perindopril, quinapril, or trandolapril) in patients with cardiovascular disease. Eligible patients were required to have either had documented echocardiographic evidence of normal left ventricular systolic function (left ventricular ejection fraction more than 40%) or had no clinical symptoms of chronic heart failure.

Outcomes of interest were incidence of all-cause mortality, cardiovascular disease mortality, fatal and non-fatal myocardial infarction, stroke, need for invasive coronary revascularisation such as percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery, hospitalisation for angina, and occurrence of new-onset diabetes mellitus.

Mean age (58 to 66 years) and percentage of female participants (14.5 to 27.5%) were similar in the included trials. However, the trials differed significantly in important baseline characteristics such as percutaneous transluminal coronary angioplasty (range 18.4 to 93%); stroke (3.4 to 10.8%); peripheral vascular disease (7.1 to 42.3%); diabetes (11.8% to 38.9%); the use of concomitant medications such as lipid lowering drugs (0.1 to 70%); and in open label angiotensin-converting enzyme inhibitor use in placebo groups (8.1 to 23%).

Two authors independently conducted the searches. It was not clear if the statement 'differences were resolved by discussion' applied to study selection.

Assessment of study quality
Trial quality was assessed using the Delphi List. Criteria included: method of randomisation, allocation concealment; similarity of groups at baseline; eligibility criteria; outcome assessor blinding; care provider blinding; patient blinding; primary outcomes with point estimates and measures of variability; and intention-to-treat analysis.

The authors stated that study quality was independently assessed, but did not provide any further details. It was not clear if the statement 'differences were resolved by discussion' applied to the validity assessment.

Data extraction
Data were extracted in order to calculate odds ratios (OR), relative risks (RR) and their associated 95% confidence intervals (CI). Trial authors were contacted for data were necessary.

The authors did not state how many reviewers performed data extraction. It was not clear if the statement 'differences were resolved by discussion' applied to the data extraction.

Methods of synthesis
Odda ratios and relative risks were combined in a meta-analysis using the Mantel Haenszel method. Only results of relative risks were presented. Heterogeneity was assessed using the Breslow-Day and Tarone’s statistics.

The number needed to treat to prevent one adverse cardiovascular disease event was also calculated.

Results of the review
Four RCTs were included in the analysis (n=31,555 participants). Trial quality appeared to be high, with all trials having adequate methods of randomisation and allocation concealment, and being triple blinded.

Compared with placebo, angiotensin-converting enzyme inhibitors were associated with a statistically significant reduction in: all cause mortality (0.87, 95% CI 0.81 to 0.94); cardiovascular mortality (RR 0.83, 95% CI 0.75 to 0.92); non-fatal acute myocardial infarction (RR 0.84, 95% CI 0.76 to 0.92); fatal and non-fatal acute myocardial infarction (RR 0.83, 95% CI 0.83 to 95% CI 0.76, 0.90); stroke (RR 0.77, 95% CI 0.67 to 0.89); need for percutaneous coronary intervention/coronary artery bypass graft (RR 0.95, 95% CI 0.90 to 0.99); hospitalisation for congestive heart failure (RR 0.78, 95% CI 0.67 to 0.90); and new-onset diabetes (RR 0.79, 95% CI 0.69 to 0.89). There was no statistically significant difference between placebo and angiotensin-converting enzyme inhibitors in terms of hospitalisation for angina.

No significant heterogeneity was found for the meta-analyses.

Authors’ conclusions
Tissue angiotensin-converting enzyme inhibitors demonstrated benefit when used for secondary prevention of cardiovascular disease in patients with preserved left ventricular function in randomised placebo-controlled trials.

CRD commentary
The review addressed a clear research question and was supported by detailed inclusion criteria. The search strategy was good, with no language restrictions, which reduced the risk of language bias. However, there were no apparent attempts to locate unpublished material, which (as the authors acknowledged) meant the risk of publication bias could not be ruled out. There was a lack of clarity regarding how many reviewers were involved in the review processes. Therefore, it is unclear if these processes were subject to reviewer error or bias.

A suitable tool was used to assess trial quality. The authors acknowledged that the trials enrolled populations with differing risks for cardiovascular disease.

The authors’ conclusion represented the evidence presented, but lack of clarity about review methods means that their reliability is unclear.

Implications of the review for practice and research
The authors did not state any implications for practice or research.

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