Tissue angiotensin-converting enzyme inhibitors for the prevention of cardiovascular disease in patients with diabetes mellitus without left ventricular systolic dysfunction or clinical evidence of heart failure: a pooled meta-analysis of randomized placebo-controlled clinical trials

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CRD summary
The authors concluded that tissue angiotensin-converting enzyme inhibitors appear to modestly reduce the risk of myocardial infarction and cardiovascular death in diabetics without left ventricular dysfunction or heart failure. The authors' cautious conclusions appear to reflect concerns about the quality of the data and thus seem appropriate.

Authors' objectives
To evaluate the effects of tissue angiotensin-converting enzyme (ACE) inhibitors on adverse cardiovascular outcomes in patients with diabetes mellitus who do not have left ventricular dysfunction or clinical evidence of heart failure.

Searching
MEDLINE (inception to November 2005), the Cochrane CENTRAL Register and the Cochrane Database of Systematic Reviews were searched for studies published in English and non-English peer-reviewed journals; the search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared the effects of tissue-selective ACE inhibitors with placebo in patients with known diabetes mellitus who had documented evidence of normal left ventricular function, or no clinical symptoms of congestive heart failure at baseline, were eligible for inclusion. Studies had to have a mean duration of follow-up of at least 12 months. The review assessed the following adverse cardiovascular outcomes: all-cause mortality, cardiovascular mortality, fatal and nonfatal myocardial infarction, stroke, hospitalisation for heart failure and the need for invasive coronary revascularisation.

The included studies evaluated ramipril (1.25 or 10 mg) and perindopril (4 or 8 mg). The characteristics of the patients varied amongst the studies; three studies were of secondary prevention and mainly included patients with documented cardiovascular or cerebrovascular disease, while the fourth study was largely a primary prevention study in patients with raised urinary albumin excretion. The median or mean duration of the included studies was about 4 years.

Three independent authors appear to have selected the studies.

Assessment of study quality
Validity was assessed using established criteria to evaluate treatment allocation, baseline comparability of the treatment groups, inclusion criteria, blinding and methods of analysis. The maximum score was 8 points.

Three reviewers independently assessed validity.

Data extraction
For each study, relative risks (RRs) of outcomes of interest were calculated with 95% confidence intervals (CIs). Authors were contacted for additional data if required.

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
Pooled RRs with 95% CIs were calculated; no further details were provided. The statistical heterogeneity of Mantel-Haenszel common odds ratios was assessed using the Breslow-Day and Tarone’s statistics. The number-needed-to-treat to avoid each outcome was calculated.

Results of the review
Four RCTs (n=10,328) were included.

All studies scored the maximum 8 points for validity.

The authors stated that no significant heterogeneity was found for any of the analyses.

ACE inhibitors were associated with a statistically significant reduction in cardiovascular mortality (RR 0.851, 95% CI: 0.741, 0.977; 4 studies; p=0.022), fatal and nonfatal myocardial infarction (RR 0.792, 95% CI: 0.685, 0.916; 3 studies; p=0.002) and the need for invasive coronary revascularisation (RR 0.860, 95% CI: 0.762, 0.971; 2 studies; p=0.015).

There was no statistically significant difference between ACE inhibitors and placebo for all-cause mortality (RR 0.913, 95% CI: 0.825, 1.011; 4 studies), stroke (RR 0.901, 95% CI: 0.761, 1.067; 4 studies) or hospitalisation for congestive heart failure (RR 0.873, 95% CI: 0.717, 1.062; 3 studies).

Authors’ conclusions
Findings suggest that tissue ACE inhibitors modestly reduce the risk of myocardial infarction and cardiovascular death in diabetics without left ventricular dysfunction or heart failure.

CRD commentary
The review question was stated clearly. Several relevant sources were searched and it seems that language restrictions were not applied. The absence of attempts to minimise publication bias might have resulted in the omission of other relevant studies. Methods appear to have been used to minimise reviewer error and bias in the study selection and validity assessment processes, but it is not clear whether similar steps were taken in the extraction of data. Only RCTs were included and validity was assessed using specified criteria. In their discussion, the authors stated that in most of the primary studies the included diabetic patients were analysed as a post hoc subgroup, that studies were open-label, and that there were problems with non-compliance and attrition. These factors all have the potential to bias review findings. The methods used for the meta-analyses seem appropriate, heterogeneity was assessed, and differences between the studies were discussed. The authors’ cautious conclusions appear to reflect concerns about the quality of the data and thus seem appropriate.

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

Research: The authors stated that newer ongoing studies will provide further evidence about the effects of tissue-selective ACE inhibitors in patients with diabetes and normal left ventricular function.

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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.