Therapeutic benefits of ACE inhibitors and other antihypertensive drugs in patients with type 2 diabetes


Authors' objectives
To assess whether angiotensin-converting enzyme (ACE) inhibitors and other hypertensive drugs are superior to alternative agents for the prevention of cardiovascular events in patients with hypertension and type 2 diabetes.

Searching
PubMed was searched to January 2000 using the following keywords: 'ACE inhibitors', 'diabetes', 'hypertension', and 'clinical trial'. The authors also checked the bibliographies of retrieved articles for additional studies, and contacted their colleagues for information on more recently published articles.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that followed patients for two or more years to allow the occurrence of a sufficient number of clinical events were eligible for inclusion. The included studies also had to be published in a peer-reviewed journal. Letters to the editor, commentaries, review articles, editorials or observational studies were excluded.

Specific interventions included in the review
Any ACE inhibitor compared with active treatment. The interventions included: enalapril (5 to 40 mg), captopril (25 to 50 mg, once or twice daily), fosinopril (20 mg), or an alternative drug such as nisoldipine (10 to 60 mg), amlodipine (10 mg), atenolol (50 to 100 mg), metoprolol (50 to 100 mg), hydrochlorothiazide (25 mg) and bendrofluazide (2.5 mg).

Participants included in the review
Patients with hypertension and type 2 diabetes who had adjudicated cardiovascular events were included. The mean age of the participants ranged from 55.0 to 63.3 years. The proportion of men in the studies ranged from 51 to 68%. The body mass index of the participants ranged from 29.7 to 31.9.

Outcomes assessed in the review
A priori outcome measures were not stated. The outcomes assessed were acute myocardial infarction, cardiovascular events, all-cause mortality and stroke.

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

Assessment of study quality
No formal assessment of quality was undertaken.

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

Data were extracted for the following categories: study identification, study design, sample size, randomised treatments, follow-up time, average age, distribution of gender, average body mass index, the proportion of participants with macroalbuminuria, the duration of diabetes, baseline systolic and diastolic arterial pressures, and the number of outcome events occurring in each treatment group.
For the combined outcome of cardiovascular events, the authors adopted the definition used in each trial. The authors calculated the total number of cardiovascular events by adding the number of fatal and nonfatal acute myocardial infarctions and strokes, the number of congestive heart failure events, and the number of sudden deaths. This method is likely to have slightly overestimated the number of patients with cardiovascular events in the UK Prospective Diabetes Study (UKPDS), because more than one event may have occurred in a single patient.

In one trial where the number of events in patients with diabetes was not reported, the authors estimated them using the sample size, the relative risk (RR), the 95% confidence intervals (CIs), and the P-value for the difference between the two treatment groups.

**Methods of synthesis**

How were the studies combined?
A pooled RR was calculated, along with 95% CIs, using the method of Peto et al. (see Other Publications of Related Interest no.1).

How were differences between studies investigated?
The differences between studies were assessed using Cochran's chi-squared statistic (see Other Publications of Related Interest no.2). In addition, to identify potential outliers, the authors tested the heterogeneity of the trial results for individual outcomes of interest through iterative analyses.

**Results of the review**

Four RCTs with 2,180 participants were included in the review: 1,133 participants were randomised to an ACE inhibitor and 1,047 were randomised to an alternative agent.

The cumulative results of 3 trials showed a statistically-significant benefit of ACE inhibitors on the outcome of acute myocardial infarction, compared with alternative treatments: there was a 63% reduction (P<0.001) and the RR was 0.37 (95% CI: 0.24, 0.57).

The cumulative results of 3 trials showed a statistically-significant benefit of ACE inhibitors on the outcome of cardiovascular events, compared with alternative treatments: there was a 51% reduction (P<0.001) and the RR was 0.49 (95% CI: 0.36, 0.67).

The cumulative results of 3 trials showed a statistically-significant benefit of ACE inhibitors on the outcome of all-cause mortality, compared with alternative treatments: there was a 62% reduction (P=0.010) and the RR was 0.57 (95% CI: 0.38, 0.87).

These findings were not observed in the UKPDS study (atenolol compared with captopril). The ACE inhibitors did not appear to be superior to other agents for the outcome of stroke in any of the trials, RR 0.76 (95% CI: 0.48, 1.22).

None of the findings were explained by differences in blood-pressure control.

The heterogeneity test was significant for both of the outcomes of acute myocardial infarction and cardiovascular events when the data of the UKPDS trial were combined with the other 3 trials (P<0.001). The heterogeneity test was not, however, significant when the UKPDS trial was excluded from the meta-analysis.

**Authors’ conclusions**
The authors state that compared with the alternative agents tested, ACE inhibitors may provide a special advantage in addition to blood-pressure control. The question of whether atenolol is equivalent to captopril remains open.

Conclusive evidence on the comparative effects of antihypertensive treatments will come from large prospective randomised trials.

**CRD commentary**
The authors stated the research question and the inclusion and exclusion criteria. The literature search was limited by searching only one database, and it was unclear whether the search was restricted to English language publications. It is possible that additional relevant studies might have been missed. Since only studies published in peer-review journals were included, there may have been publication bias, e.g. one unpublished Swedish trial was excluded. The quality of the included studies was not formally assessed and the authors did not report how the articles were selected, or who performed the selection and data extraction.

The data extracted were reported in tables and discussed in the text of the review. The studies were combined in a statistical meta-analysis and heterogeneity was assessed. Further analyses were performed to assess the effects of differences between the studies, and this established that one of the four trials caused the heterogeneity. The authors’ conclusions appear to follow from the results, but should be viewed with caution because of limitations in the quality of the review process.

Implications of the review for practice and research

Practice: The authors state that it may be prudent to use ACE inhibitors as a first-line agent for the treatment of hypertension in patients with type 2 diabetes.

Research: The authors state that further large prospective randomised trials are needed to assess the comparative effects of antihypertensive treatments.

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