Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on all-cause mortality, cardiovascular deaths, and cardiovascular events in patients with diabetes mellitus: a meta-analysis
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CRD summary
The authors concluded that ACEIs reduced all-cause mortality, cardiovascular mortality and major cardiovascular events in patients with diabetes mellitus whereas ARBs had no beneficial effects on these outcomes. These conclusions reflect the evidence presented and appear reliable.

Authors’ objectives
To evaluate the effects of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) on all-cause mortality, cardiovascular deaths and major cardiovascular events in people with diabetes mellitus.

Searching
MEDLINE, EMBASE and Cochrane CENTRAL were searched to December 2012; search terms were reported. Abstracts from American Diabetic Association meetings between 2005 and 2012, reference lists and ClinicalTrials.gov were searched. No language restrictions were applied.

Study selection
Eligible trials were randomised controlled trials that compared ACEIs or ARBs (any dose or type) with placebo, no treatment or other antihypertensive drugs (including ACEIs or ARBs) in people with diabetes mellitus. Trials that reported post hoc and subgroup analyses for people with diabetes mellitus were included. Trials had to report cardiovascular death or all-cause mortality outcomes with at least a 12-month mean or median follow-up.

The ACEIs studied were enalapril, captopril, perindopril, fosinopril, ramipril and lisinopril; ARBs studied were candesartan, telmisartan, losartan, irbesartan and olmesartan. Active treatment comparisons were nifedipine, nisoldipine, amlodipine, atenolol and enalapril. Most studies were of people with type 2 diabetes. In six studies none of the participants had hypertension at baseline. Mean age of participants ranged from 29 to 76 years. Follow-up ranged from 12 to 108 months.

Two reviewers independently selected trials for inclusion.

Assessment of study quality
Study quality was assessed in terms of allocation concealment, intention-to-treat analysis, blinding of investigators, participants and outcome assessors, and completeness of follow-up. The Jadad scale was also used.

Two reviewers independently assess study quality.

Data extraction
Data to calculate risk ratios with 95% confidence intervals were extracted for all-cause mortality, cardiovascular deaths and a composite measure of major cardiovascular events (cardiovascular death, non-fatal myocardial infarction, stroke, congestive heart failure and coronary artery bypass graft or percutaneous coronary intervention). Outcomes were based on the longest follow-up period available for each study.

The authors did not state how many reviewers extracted data.

Methods of synthesis
A random-effects model was used to pool risk ratios. Results were confirmed by a Mantel-Haenszel fixed-effect model. Primary analyses were done after stratifying studies based on comparator (placebo versus active treatment). Heterogeneity was assessed using the I² statistic. Publication bias was assessed by funnel plot and Begg test. Subgroup analyses were used to explore heterogeneity related to participants, agent used and trial quality.
Results of the review
Thirty-five randomised controlled trials (56,444 participants, range 32 to 11,140) were included reporting 11 comparisons of ACEIs with placebo/no treatment, 12 comparisons of ACEIs with active treatment, 10 comparisons of ARBs with placebo and three comparisons of ARBs with active treatment. Study quality was generally good: 60% of studies had a Jadad score greater than 3 and 17 studies scored 5 (the maximum possible). Half of the studies met the allocation concealment criteria (details not reported for the other studies).

ACEIs: Compared with control (placebo or active treatment), ACEIs were associated with a statistically significant reduction in all-cause mortality (RR 0.87, 95% CI 0.78 to 0.98; 20 studies; I²=26%), cardiovascular deaths (RR 0.83, 95% CI 0.70 to 0.99; 13 studies; I²=40%) and major cardiovascular events (RR 0.86, 95% CI 0.77 to 0.95; 14 studies; I²=59%). Results were similar when ACEIs were compared with placebo or active treatment.

There was no evidence that the observed effects on all-cause mortality and cardiovascular deaths differed by subgroups including baseline blood pressure and type of diabetes. There was no evidence of publication bias for all-cause mortality.

Results were reported for cause-specific cardiovascular outcomes (myocardial infarction, heart failure and stroke).

ARBs: Compared with control (placebo or active treatment), there was no statistically significant effect on all-cause mortality (RR 0.94, 95% CI 0.82 to 1.08; 11 studies; I²=22%), cardiovascular deaths (RR 1.21, 95% CI 0.81 to 1.80; seven studies; I²=61%) and major cardiovascular events (RR 0.94, 95% CI 0.85 to 1.01; nine studies; I²=13%). Results were similar when ARBs were compared with placebo or active treatment.

There was insufficient data to allow meta-regression and subgroup analysis.

Results were reported for cause-specific cardiovascular outcomes (myocardial infarction, stroke and heart failure).

Authors’ conclusions
ACEIs reduce all-cause mortality, cardiovascular mortality and major cardiovascular events in patients with diabetes mellitus, whereas ARBs have no beneficial effects on these outcomes.

CRD commentary
The review question and inclusion criteria were clear. The authors attempted to identify all relevant studies in any language by searching electronic databases and checking references and abstracts of relevant meetings. Study selection and quality assessment were undertaken in duplicate to minimise bias; the process for data extraction was unclear.

Study quality was evaluated and the results were used in the subgroup analyses. A random-effects model was appropriate as there was significant heterogeneity for some outcomes. Possible explanations for statistical heterogeneity were explored. The authors appropriately noted that their analysis could not confirm whether ACEIs were superior to ARBs in terms of survival in patients with diabetes mellitus.

The authors’ conclusions reflect the evidence presented and appear reliable.

Implications of the review for practice and research
Practice: The authors stated that ACEIs should be considered as first-line therapy to limit excess mortality and morbidity in patients with diabetes mellitus.

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

Funding
National Basic Research Program of China; Zhejiang Provincial Education Department, China.

Bibliographic details
Database of Abstracts of Reviews of Effects (DARE)
Produced by the Centre for Reviews and Dissemination
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