Comparative effectiveness of renin-angiotensin system blockers and other antihypertensive drugs in patients with diabetes: systematic review and Bayesian network meta-analysis

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CRD summary
The analyses suggested renal protective effects and superiority for angiotensin-converting enzyme inhibitors, compared with other classes of antihypertensive drug, for patients with diabetes. These conclusions are likely to be a reliable summary of the published evidence.

Authors' objectives
To assess the effects of different classes of antihypertensive drugs, alone or in combination, on survival and major renal outcomes for patients with diabetes.

Searching
PubMed, Scopus, and The Cochrane Library were searched for peer-reviewed studies, published up to December 2011; search strategies were reported in an appendix. There were no language restrictions. The reference lists of all identified studies were searched.

Study selection
Parallel-group randomised trials were eligible if they compared any single antihypertensive drug, or combination of drugs, with placebo or with other classes of active treatment, for adults (over 18 years old) with any type of diabetes. Trials had to follow patients up for at least 12 months, and to report at least one of the following outcomes: all-cause mortality, end-stage renal disease (need for dialysis or kidney transplant), or doubling of serum creatinine levels.

In the included trials, patients were randomised to receive: angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium-channel blockers, angiotensin-receptor blockers, diuretics, combinations of these, or placebo. The mean age ranged from 20 to 66 years. All types of diabetes were studied, but most trials were of patients with type 2 diabetes. Almost all trials reported mortality; only around a quarter of them reported end-stage renal disease and doubling of serum creatinine. The trial results were published between 1989 and 2011.

The authors did not state how many reviewers selected the trials.

Assessment of study quality
Two reviewers independently evaluated trial quality, using the Cochrane risk of bias tool, for sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Disagreements were resolved by discussion, or by consensus with two senior reviewers.

Data extraction
Two reviewers independently extracted the data to calculate odds ratios. Trial authors were contacted for clarification, if necessary.

Methods of synthesis
Standard meta-analyses, and Bayesian network meta-analyses were performed. The standard analyses used a random-effects model to calculate the pooled odds ratios, with 95% confidence intervals; heterogeneity was assessed using $I^2$ and Cochran's Q. Publication bias was evaluated in funnel plots and Begg's and Egger's tests.

For the network meta-analysis, a random-effects model and Monte Carlo, Markov chains were used to calculate odds ratios, with 95% credible intervals. The node splitting method was to calculate the inconsistency of the model.

Sensitivity analyses were performed by excluding trials with few patients or events, or trials with large samples. Treatments were ranked, and the probability that each treatment was best was calculated.
Results of the review
Sixty-three trials (36,917 participants) were included. Sample sizes ranged from 11 to 11,140. Most trials were judged to be at a low risk for many bias domains, but the risk was unclear, in most trials, for sequence generation and allocation concealment. Follow-up ranged from one to six years.

Network analyses: Only ACE inhibitors (2,819 patients) significantly reduced the doubling of serum creatinine levels, compared with placebo (OR 0.58, 95% CrI 0.32 to 0.90), and compared with beta blockers (OR 0.12, 95% CrI 0.02 to 0.74). Compared with placebo, only beta blockers (71 patients) showed a significantly increased mortality (OR 7.13, 95% CrI 1.37 to 41.39). There were no statistically significant differences between treatments, for end-stage renal disease.

Compared with angiotensin-receptor blockers, ACE inhibitors consistently showed higher probabilities of being ranked better for all three outcomes. For mortality, the protective effect of an ACE inhibitor plus calcium-channel blocker, compared with placebo, was not statistically significant, but this had the greatest probability (0.739) of being the best treatment. ACE inhibitors with diuretics had the highest probability (0.460) of being the next best treatment.

There was no evidence of significant inconsistency within the networks for any of the three outcomes.

Standard analyses: Although the point estimates showed small differences, the confidence intervals, as well as the credible intervals from the network meta-analyses, generally overlapped. No heterogeneity and no publication bias were identified.

Authors’ conclusions
The analyses showed the renal protective effects and superiority of ACE inhibitors for patients with diabetes, and did not show a better effect for angiotensin-receptor blockers. Considering the costs of the drugs, this supported ACE inhibitors as the initial antihypertensive treatment for patients with diabetes.

CRD commentary
The review addressed a clear question and was supported by reproducible eligibility criteria. Several relevant databases were searched, but only for published studies, meaning that some relevant trials may have been missed. There was no indication that publication bias affected the results. Independent duplicate processes were used to reduce the risks of reviewer error and bias, except that they were not reported for the screening process.

The risk of bias was assessed; the trials were judged to be at low-to-moderate risk, and the authors used these results to make a recommendation for further research. Adequate details of the trials were provided. A network analysis was used to pool their data. This combined direct and indirect data for the treatment comparisons. The results can be less reliable, but this analysis found no evidence of inconsistency between the network and the standard meta-analyses. Many of the included trials were small and reported few, or no events.

The authors’ conclusions are a fair reflection of the published evidence, and they are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that, considering the costs of the drugs, ACE inhibitors should be the first antihypertensive treatment for patients with diabetes. Calcium-channel blockers could be added, if adequate blood pressure control could not be achieved with the ACE inhibitors alone.

Research: The authors stated that more research was needed into the effects of patient characteristics and trial method quality on the treatment outcomes.

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