Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials

Blood Pressure Lowering Treatment Trialists’ Collaboration

CRD summary
This review found that blood pressure lowering was effective in preventing cardiovascular events, in people with a moderately reduced glomerular filtration rate. This was a large meta-analysis based on individual patient data, and its findings are very likely to be reliable.

Authors’ objectives
To define the cardiovascular effects of lowering blood pressure, in people with and those without chronic kidney disease.

Searching
This was a collaborative prospective review. No formal search was described, but new trials were sought through literature searches (databases not reported), searches of abstracts and proceedings of meetings, and contact with relevant experts and drug manufacturers.

Study selection
Any randomised controlled trial (RCT) that either compared a blood pressure lowering treatment with a control, or compared different blood pressure lowering treatments, was eligible. Trials had to have a minimum of 1,000 patient-years of follow-up for each group, and to have presented or published their results after July 1995. The main outcome was any major cardiovascular event (defined in the paper). Other outcomes were stroke, coronary heart disease, heart failure, cardiovascular death, and mortality.

Most of the included trials recruited patients with high blood pressure or existing cardiovascular disease. Treatments included angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, calcium antagonists, and diuretics. The average patient age ranged from 50 to 77 years; the percentage of men ranged from six to 92. Average systolic blood pressure ranged from 127 to 194 millimetres of mercury (mmHg), and the average creatinine level ranged from 62 to 183 millimoles per litre. Eighty percent of participants had an estimated glomerular filtration rate of 60mL/min/1.73m² or higher. Where recorded, 7% of participants had proteinuria.

The process of selection of trials was not described.

Assessment of study quality
Trial quality was assessed using the Cochrane Collaboration’s risk of bias tool. The number of reviewers who performed the assessment was not stated.

Data extraction
Individual patient data (IPD) for each participant were sought from the principal investigator of each trial. Where IPD were unavailable, summary results, including numbers of cardiovascular events, hazard ratios for outcomes, and average blood pressure reductions, were sought. Kidney function was classified, using the estimated glomerular filtration rate (eGFR).

How the data were extracted, checked, and managed was not described.

Methods of synthesis
For each trial, and for each outcome, hazard ratios with their 95% confidence intervals, for the effect of treatment, were calculated using Cox proportional hazards models, or odds ratios were calculated using logistic regression. The results were synthesised across trials, using DerSimonian and Laird random-effects meta-analyses.

Subgroup analyses and meta-regression were used to investigate the effects of baseline glomerular filtration rate, blood
pressure reductions achieved, and the presence of proteinuria. Heterogeneity was estimated using Cochran’s Q and \( I^2 \).

Publication bias was assessed using Egger's and Begg’s tests.

**Results of the review**

There were 25 trials in the review, with 152,290 participants. The trials were at a low risk of bias, although some did not use blinding. Follow-up times ranged from two to 8.4 years.

ACE inhibitors, compared with placebo, reduced the risk of major cardiovascular events (HR 0.81, 95% CI 0.73 to 0.90). Calcium antagonists were also more effective than placebo (HR 0.72, 95% CI 0.58 to 0.89). For each 5mmHg reduction in systolic blood pressure achieved, both types of drug reduced the risk of events by about 17% (both drugs combined HR 0.83, 95% CI 0.79 to 0.87).

There was no evidence that more intensive blood pressure lowering was more effective than less intensive therapy. There was also no evidence of a difference in effectiveness between different classes of blood pressure lowering drugs (full results presented).

There was no evidence that the glomerular filtration rate altered the effectiveness of treatment, but the absolute effect was greater in people with rates less than 60mL/min/1.73m\(^2\) (NNT 35), than in those with higher rates (NNT 53). The presence of proteinuria was not found to alter the effectiveness of treatment.

There was some evidence of publication bias (Egger’s test p=0.05), but further analysis did not suggest that this materially affected the results. Further results, including those for secondary outcomes, were reported.

**Authors’ conclusions**

Blood pressure lowering was effective in preventing cardiovascular events in people with a moderately reduced glomerular filtration rate. There was little evidence to support a preference for any particular drug class.

**CRD commentary**

This was generally a well-conducted prospective individual patient data meta-analysis. The review question was medically relevant and suitable inclusion criteria were used. There were some limitations in reporting, particularly around how the trials were identified and how the raw data were checked and managed. Whether or not all relevant trials were included, and if reviewer error was avoided, were therefore unclear.

The review included a large number of randomised trials and participants. The risk of bias in the trials was judged to be low, but not all trials used blinding. The raw data were available for most of the included trials, and a thorough meta-analysis of these data was conducted.

The large size of this collaborative review, and the thorough analysis, suggest that the results are reliable, and the authors’ conclusions are appropriate.

**Implications of the review for practice and research**

**Practice:** The authors suggested that the wider use of blood pressure lowering and lipid lowering drugs should reduce the burden of cardiovascular disease.

**Research:** The authors made no recommendations for future research.

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