Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials

CRD summary
This review assessed the effect of treatments that reduce blood pressure in patients receiving dialysis. The authors concluded that treatments which lower blood pressure reduced cardiovascular morbidity and mortality in patients receiving dialysis. The author's conclusions reflected the evidence presented and were likely to be reliable.

Authors' objectives
To assess the effects of treatments that reduce blood pressure in patients receiving maintenance dialysis.

Searching
MEDLINE (1950-November 2008), EMBASE (1966 - November 2008) and the Cochrane Register of Controlled Trials (no date restriction) were searched without language restrictions to identify relevant studies. Search terms were reported. The reference lists of identified studies and of relevant review articles were scanned. The website ClinicalTrials.gov was searched for completed but unpublished studies. Requests for original data were sent to authors and principal investigators.

Study selection
All completed randomised controlled trials (RCTs) that assessed the effects of agents that lower blood pressure on cardiovascular outcomes in adult patients receiving maintenance dialysis were eligible for inclusion in the review. Outcomes of interest were: all cardiovascular events as defined by the authors of each study; all-cause mortality; and cardiovascular mortality. Blood pressure lowering agents varied between the studies and included: beta blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and calcium channel blockers. Between the studies mean age varied from 55 to 67 years and the percentage of males from 52 per cent to 63 per cent. Two independent reviewers selected the studies for inclusion in the review. It was not reported how disagreements were resolved.

Assessment of study quality
Study quality was assessed using the criteria of allocation concealment, similarity of groups at baseline in terms of prognostic factors, eligibility criteria, blinding of outcomes assessors, completeness of follow up and the use of intention to treat (ITT) analysis. The Jadad scale was used as a quantitative assessment. Two reviewers assessed study quality. Disagreements were resolved by a third reviewer.

Data extraction
Data was extracted in order to calculate risk ratios (RR) with 95% confidence intervals (CI) for dichotomous outcomes and mean differences for systolic and diastolic blood pressure. Two independent reviewers performed the data extraction. Disagreements were resolved by a third reviewer.

Methods of synthesis
Pooled RRs and weighted mean differences (WMDs) were calculated using a random-effects (DerSimonian and Laird) model meta-analysis. Heterogeneity was assessed using the $I^2$ test and the Q statistic. Potential sources of heterogeneity were explored using univariate meta regression. In order to identify causes of heterogeneity, subgroup analyses were performed according to number of events, duration of follow-up, patient status and class of blood pressure lowering agent used. Sensitivity analysis was performed by excluding unpublished studies. Publication bias was assessed using the Egger's test and Begg's funnel plots.

Results of the review
Eight RCTs were included in the meta analysis (n=1,679 patients). Sample sizes ranged from 60 to 397 patients. The mean Jadad score was 3.1 (range 2-5). Publication bias was reported to be absent. Overall treatment with blood pressure lowering drugs was associated with a lower risk of cardiovascular events compared with control (RR 0.71, 95% CI:
0.55, 0.92, p=0.009). However, there was evidence of statistically significant heterogeneity ($I^2$: 67.5%, Q statistic: 21.5, p=0.003). Subgroup analyses were not statistically significant with the exception of admission to hospital for heart failure as a cardiac event ($I^2$ and Q statistic value not reported, p=0.006).

Blood pressure lowering treatments were also associated with a lower risk of all-cause mortality (RR 0.80, 95% CI: 0.66, 0.96, p=0.014, seven RCTs) and of cardiovascular mortality (RR 0.71, 95% CI: 0.50, 0.99, p=0.044, five RCTs) compared with control with no evidence of statistically significant heterogeneity.

**Authors’ conclusions**
Treatment with agents that lower blood pressure reduced cardiovascular morbidity and mortality in patients on maintenance dialysis.

**CRD commentary**
This review addressed a clear research question and was supported by detailed inclusion criteria. The search strategy was adequate and included studies in languages other than English, which would reduce the possibility of language bias. The Egger test and Begg’s funnel plots revealed no evidence of publication bias. The validity assessment tool was appropriate for the included study designs. Adequate details of the primary studies were provided and synthesis methods were appropriate. Subgroup analyses were performed in order to determine sources of statistically significant heterogeneity. The review process was carried out with sufficient attempts to minimise errors and bias. The authors’ conclusions reflected the evidence presented and were likely to be reliable.

**Implications of the review for practice and research**
Practice: The authors stated that treatment with agents that lower blood pressure should routinely be considered for individuals undergoing dialysis to reduce the very high cardiovascular morbidity and mortality rate in this population.

Research: The authors stated that randomised controlled trials that compare the effects of different intensities of blood pressure lowering on the risk of subsequent cardiovascular outcomes in patients on dialysis would provide further insight.

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