Cardiovascular protection with antihypertensive drugs in dialysis patients: systematic review and meta-analysis
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CRD summary
This review suggested that treatment of haemodialysis patients with antihypertensive drugs offered a benefit in terms of cardiovascular protection. The authors acknowledged review data limitations and potential risk from publication bias; despite this, their conclusions seemed somewhat overstated and, therefore, their findings should be regarded with caution.

Authors' objectives
To assess the cardiovascular protective effects of antihypertensive drugs in patients who underwent long-term dialysis.

Searching
PubMed (from January 1996), EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to October 2008. Search terms were reported. Reference lists of retrieved articles and reviews were screened for additional studies, as were with proceedings of American Society of Nephrology and European Dialysis and Transplantation Association. The authors did not report whether they used any language limitations.

Study selection
Randomised controlled trials (RCTs) of antihypertensive therapy in patients who underwent long-term dialysis treatment were eligible for inclusion in the review. Eligible outcomes were cardiovascular event rates and all-cause mortality.

Included studies assessed the following treatments: fosinopril, candesartan, angiotensin receptor blockers (ARBs), carvedilol and amlodipine. Exposure to treatment ranged from 19 months to 36 months. Comparators were placebo or no treatment. Normotensive drugs were used in 60% of the studies. Included participants ranged in mean age from 55 to 67 years. Mean baseline blood pressure ranged from 134/75mmHg to 156/82mmHg.

The authors state neither how papers were selected for review nor how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The number of deaths and cardiovascular events for the intervention and control groups were extracted and used to calculate risk ratios (RRs) with 95% confidence intervals (CIs). Hazard ratios (HRs) with 95% CIs were extracted and used to calculate log hazard ratios.

The authors stated neither how data were extracted for the review nor how many reviewers performed the data extraction.

Methods of synthesis
Pooled risk ratios and hazard ratios with 95% CIs were calculated using both fixed-effect and random-effects models. Statistical heterogeneity was assessed visually by observing Forest plots and quantified using $I^2$. Analyses were repeated sequentially excluding one study at a time to assess the influence of each individual study. A sensitivity analysis was used to assess the influence of hypertensive status (hypertensive patients only versus populations that also included normotensive patients). Publication bias was assessed using an Egger's test and a funnel plot.

Results of the review
Six RCTs (n=1,202) were included in the review. Sample sizes ranged from 80 to 397.

The pooled hazard ratio for cardiovascular events showed a statistically significant difference in favour of antihypertensive drugs (0.69, 95% CI 0.56 to 0.84 using a fixed-effect model). However, there was evidence of significant statistical heterogeneity ($I^2=50.4\%$, $p=0.073$). Risk ratios for cardiovascular events and all-cause mortality also significantly favoured antihypertensive drugs.

Evidence from sensitivity analyses suggested that there was a significant difference ($p<0.006$) between studies that assessed only hypertensive patients and those that assessed populations that also included normotensive patients (HR 0.49, 95% CI 0.35 to 0.67; three studies for hypertensive patients only and HR 0.86, 95% CI 0.67 to 1.12; three studies for hypertensive and normotensive patients). Similar findings were reported when risk ratios were assessed for cardiovascular events, but differences were not statistically significant for all-cause mortality.

Egger's test and funnel plot suggested that there was a significant risk of publication bias.

**Authors' conclusions**
This review suggested that treatment of haemodialysis patients with antihypertensive drugs offered a benefit in terms of cardiovascular protection.

**CRD commentary**
This review answered a clear research question. There was some suggestion of publication bias, although this evidence was based on only a small number of studies and so may not be reliable. The risk of reviewer error and bias was unclear as the review processes were not adequately described. No assessment of study quality was carried out and so the reliability of data was unclear; a number of the studies were based on only small sample sizes, which suggested that data may not reliable. Pooled effect sizes were calculated despite evidence of statistical heterogeneity. Further analyses failed to adequately explain the source of this bias; the statistical power of these analyses was likely to be low given the small number of studies included in the review. Results from both fixed-effect and random-effects models were reported. Cardiovascular events were not defined in each study. The authors acknowledged the data limitations and risk from publication bias, but their conclusions on the beneficial effects of antihypertensive therapy seemed somewhat overstated given such limitations and the findings should be regarded with caution.

**Implications of the review for practice and research**
- **Practice:** The authors stated that evidence from the randomised controlled trials included in this review suggested that treatments for hypertension should be used among hypertensive patients who underwent haemodialysis.
- **Research:** The authors stated that that further trials using out-of-dialysis unit blood pressure monitoring were required to further show the benefit of lowering blood pressure in the high-risk population of patients who underwent dialysis. Future trials should be adequately powered and include an assessment of left ventricular mass and function to further refine cardiovascular risk assessment and investigate the management of hypertension.

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