Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis

CRD summary
This generally well-conducted review concluded that intensive blood pressure lowering regimens appeared to provide protection against kidney failure events in patients with chronic kidney disease, particularly among those with proteinuria; safety remained an uncertainty. The strength of evidence did not support strong conclusions on renal outcomes and the authors conclusions may be overly strong.

Authors’ objectives
To assess the renal and cardiovascular effects of intensive blood pressure lowering in people with chronic kidney disease.

Searching
MEDLINE, EMBASE and Cochrane Central register of Controlled Trials (CENTRAL) were searched for studies published between 1950 and July 2011. There were no language restrictions. Search terms were reported. Reference lists from included trials and review articles and ClinicalTrials.gov were searched.

Study selection
Randomised controlled trials (RCTs) with at least six months follow-up that compared intensive and standard antihypertensive regimens (classified based on target blood pressure levels) in patients with chronic kidney disease (Kidney Disease Outcomes Quality Initiative definition) were eligible for inclusion. Trials had to report incidences of kidney failure and/or cardiovascular events. The primary outcome was a composite of 50% decline in glomerular filtration rate and doubling of the serum creatinine level, or end-stage kidney disease; end-stage kidney disease was also reported as a separate outcome.

Blood pressure targets varied substantially across trials. Mean age of patients ranged from 12 to 74 years and 26% to 64% of the participants were women. Where reported, approximately one third of the studies excluded patients with diabetes and another third restricted inclusion to this subgroup.

Two reviewers independently selected studies for the review.

Assessment of study quality
Two reviewers independently assessed study quality using the Cochrane risk of bias tool.

Data extraction
Two reviewers independently extracted data to calculate hazard ratios (HR) for time dependent outcomes and mean differences for continuous outcomes, each with 95% confidence intervals (CI). Relative risks (RR) were extracted where hazard ratios were not available. Data had to be reported separately for patients with chronic kidney disease in trials with mixed populations. Differences were resolved by discussion or referral to a third reviewer. Trial authors were contacted for additional information where necessary.

Methods of synthesis
Pooled hazard ratios, risk ratios or weighted mean differences (WMD) were calculated along with their 95% CI using the DerSimonian-Laird random-effects model. Heterogeneity was assessed using the I² statistic. Subgroup analyses investigated the impact of baseline proteinuria. Patient age, duration of follow-up, sample size, event number, baseline glomerular filtration rate and trial quality were also investigated but this was not prespecified in the methods. Publication bias was investigated using funnel plots.

Results of the review
Eleven RCTs (9,287 patients with chronic kidney disease, range 75 to 3,619) met the inclusion criteria. Four RCTs did
not describe allocation concealment, two trials blinded patients, six trials blinded outcome assessors, five trials used intention-to-treat analysis and seven trials had less than 10% of incomplete outcome data; none reported blinding investigators. Follow-up ranged from 1.6 to 16.7 years.

Compared with standard antihypertensive regimens (seven RCTs, 5,308 patients), intensive strategies significantly reduced the risk of doubling of serum creatinine level/50% decline in glomerular filtration rate/end-stage kidney disease (HR 0.82, 95% CI 0.68 to 0.98; I²=38.1%) and end-stage kidney disease (HR 0.79, 95% CI 0.67 to 0.93; I²=21.6%); there was no evidence for publication bias. Baseline proteinuria, allocation concealment and blinding of outcome assessors were shown to have significant impact on the results. There was no significant difference between regimens on the risk of cardiovascular events (five RCTs, 5,308 patients), stroke (six RCTs, 5,411 patients), myocardial infarction (five RCTs, 4,317 patients), heart failure (five RCTs, 5,308 patients) and death (10 RCTs, 6,788 patients).

Adverse events: There was no significant difference between regimens on severe adverse events (two RCTs, 723 patients), hypotension (three RCTs) and treatment discontinuation (three RCTs); none of the trials reported on the risk of acute kidney injury.

Authors’ conclusions
Intensive blood pressure lowering appeared to provide protection against kidney failure events in patients with chronic kidney disease, particularly among those with proteinuria. Safety of such intensive regimens remained an uncertainty and effects remained to be shown in people with normal urinary protein excretion.

CRD commentary
The review addressed a clear research question supported by reproducible inclusion criteria. Relevant sources were searched for published and ongoing trials without language restrictions; unpublished trials were not sought. Each stage of the review was conducted in duplicate and this reduced risks of error and bias. Appropriate criteria were used to assess study quality and the results were investigated within the analysis. There was substantial clinical heterogeneity across the RCTs and most had methodological flaws. The two main analyses on which the conclusion was based included heterogeneous trials often with imprecise results (the imprecision could impact on the results of the I² with heterogeneity greater than indicated). Both analyses could be influenced by the addition of another good quality trial, which if it showed no effect could make the overall pooled result non-significant.

This was generally a well-conducted review but the strength of evidence did not support strong conclusions on renal outcomes and the authors conclusions may be overly strong.

Implications of the review for practice and research
Practice: The authors stated that the results of the review provided support for guidelines that suggested lowering blood pressure targets in people with proteinuric chronic kidney disease and highlighted the potential value of this approach.

Research: The authors stated that more data were required to determine the effect of such a strategy in patients without proteinuria.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.