Renin angiotensin system blockade and cardiovascular outcomes in patients with chronic kidney disease and proteinuria: a meta-analysis


CRD summary
The authors concluded that among patients with chronic kidney disease from any cause, renin angiotensin system blockade reduced myocardial infarctions, heart failure and overall cardiovascular adverse events compared with placebo. The conclusions may need to be interpreted cautiously due to the small number of studies included in the main analyses, unexplained heterogeneity and inconsistent findings across different clinical outcomes.

Authors' objectives
To determine the effects of renin angiotensin system (RAS) blockade on cardiovascular (CV) outcomes among patients with chronic kidney disease (CKD) and proteinuria.

Searching
MEDLINE, EMBASE and two or three unnamed databases were searched for peer-reviewed studies published between 1975 and 2006. Search terms were reported. Published meta-analyses and reviews were handsearched. Ongoing trials were sought in three websites (www.clinicaltrials.gov, www.act.org.au and www.controlled-trials.gov). The search was limited to studies in English.

Study selection
Randomised controlled trials (RCTs) comparing angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACE/ARB) versus active controls or placebo were eligible for inclusion, provided they were conducted among patients with at least (≥) stage two CKD as defined by the Kidney Disease Outcomes Quality Initiative guidelines. Trials were required to report CV outcomes as primary, secondary or adverse outcomes.

The studies in the review included diabetic, non-diabetic, hypertensive and normotensive patients with ≥stage 2 CKD or proteinuria. Mean glomerular filtration rate varied widely. ACE inhibitors or ARB were compared with beta-blockers, calcium-channel blockers and other antihypertensive therapy. Most studies used more than one antihypertensive drug (for example, diuretics). Many different ACE/ARB drugs and comparator drugs were used. Primary outcomes differed widely across the studies. Few studies reported CV outcomes as primary or secondary endpoints. Outcomes reported in the review were CV outcomes (all adverse CV events, including coronary revascularisation and unstable angina), myocardial infarction (MI), stroke, heart failure, CV mortality and all-cause mortality. The weighted mean duration of follow up was 56.2 months (range 20 weeks to 6.4 years).

Two reviewers independently selected trials for inclusion. Disagreements were resolved by discussion.

Assessment of study quality
The validity criteria considered were: treatment allocation, allocation concealment, blinding and use of intention to treat analysis. The assessment was conducted independently by two reviewers.

Data extraction
Risk ratios (RRs) were calculated from the numbers of events in the control and intervention groups of each study, with 95% confidence intervals (CIs). Data were extracted using a standardised format. Primary investigators were contacted to request unpublished data. The authors stated neither how papers were selected for the review nor how many reviewers performed the selection.

Methods of synthesis
Data were combined using random and fixed effects Mantel-Haenszel models to calculate pooled RRs and 95% CIs, grouped by CKD aetiology. The results of fixed effect models were reported in the review. Heterogeneity was assessed using the X^2 statistic. Publication bias was assessed with a funnel plot and Egger’s test. Regression analyses investigated the impact of a range of demographic, clinical and methodological differences between the studies. Where a single
study dominated a subgroup, it was reanalysed without the dominating study.

Results of the review
Twenty-five RCTs were included (n=45,758): nine placebo controlled (n=17,357) and 16 with active controls (n=28,401). Twenty-three were prospective and two were post-hoc analyses. All were double-blinded and used intention to treat analysis. Twenty-four RCTs were described as double-blinded.

All nephropathy: there was no statistically significant difference between the groups for any outcome when RAS blockade was compared with active control therapy (nine RCTs). However, there was a non-significant trend for RAS to increase the risk of stroke compared to active controls (p=0.05, five RCTs). RAS blockade significantly reduced the risk of overall CV events (RR 0.84, 95% CI: 0.78, 0.91, p=0.0001, five RCTs), heart failure (RR 0.74, 95% CI: 0.58, 0.95, p=0.02, two RCTs) and MI (RR 0.78, 95% CI: 0.65, 0.97, p=0.03, five RCTs) compared to placebo. But, there was statistically significant heterogeneity in the findings for overall CV events (p=0.02).

Proteinuria: RAS significantly reduced the risk of overall CV events (p=0.04, 10 RCTs) and heart failure (p=0.009, three RCTs) compared to active controls and significantly reduced the risk of heart failure compared to placebo (p=0.005, two RCTs).

Diabetic nephropathy: RAS significantly reduced the risk of heart failure compared to active controls (p=0.003, three RCTs) and significantly reduced the risk of overall CV events (p=0.009, six RCTs) and heart failure (p=0.003, three RCTs) compared to placebo. There was some indication of publication bias for these findings.

Non-diabetic nephropathy: RAS significantly reduced the risk of overall CV events and heart failure compared to active controls (p=0.001, eight RCTs).

Hypertensive nephropathy: there was a non-significant trend for RAS to increase the risk of stroke compared to active controls (p=0.05, four RCTs).

Full RRS and 95% CIs were reported for all the above comparisons. The results of other reported comparisons were not statistically significant.

Subgroup and sensitivity analyses reported no significant findings.

Authors’ conclusions
Among patients with CKD from any cause, RAS blockade reduced myocardial infarctions, heart failure and overall CV adverse events compared with placebo. Among patients with proteinuria, RAS reduced the risk of CV adverse events and heart failure compared with active control therapy.

CRD commentary
The objectives and inclusion criteria of the review were clear in most respects, though the distinction between CKD and proteinuria (if any) was not clearly defined. Some relevant sources were searched for studies, and efforts were made to retrieve unpublished data, but some databases searched were not named. The restriction to studies in English meant that the review was prone to language bias. Steps were taken to minimise the risk of bias and error by having more than one reviewer independently undertake study selection and validity assessment, but less detail was provided about the process of data extraction. Adequate information was provided about the included studies. Relevant criteria were used to assess validity. Statistical techniques used to pool data and assess for heterogeneity and publication bias appeared appropriate, but the reasons for the statistical heterogeneity detected were not explored adequately. Moreover, few of the included studies reported CV events as primary or secondary outcomes, which reduced confidence in the reliability of the data. The authors’ conclusions may need to be interpreted cautiously due to the small number of studies included in the main analyses, unexplained heterogeneity and inconsistent findings across different clinical outcomes.

Implications of the review for practice and research
Practice: the authors stated that RAS blockade agents should be first choice for patients with diabetic nephropathy and proteinuria.

Research: the authors did not state any implications for research.
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