Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin-angiotensin system on proteinuria in renal disease

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CRD summary
This review assessed the effects of angiotensin-receptor blockers (ARBs) on urinary protein excretion in patients with nephropathy. It concluded that ARBs reduce proteinuria and the combination of an ARB plus an angiotensin-converting enzyme inhibitor is more effective than either drug alone. This was a well-conducted review with reliable conclusions, but the inclusion of only studies published in English might have introduced bias.

Authors' objectives
To evaluate the effect of angiotensin-receptor blockers (ARBs) and combined treatment with ARBs and angiotensin-converting enzyme (ACE) inhibitors on proteinuria.

Searching
MEDLINE and the Cochrane CENTRAL Register (Issue 3, 2006) were searched from January 1990 to September 2006; the search terms were reported. Only English language articles were included in the review. In addition, reference lists were screened and experts in the field contacted.

Study selection
Randomised controlled trials (RCTs) of parallel or crossover design, which compared ARBs with placebo, ACE inhibitors or other antihypertensive drugs, were eligible for inclusion. Studies had to have a minimum duration of 4 weeks and at least 10 participants. Studies of combined therapy with ARBs plus an ACE inhibitor compared with either drug individually were also eligible. Studies comparing different doses of the same drug were excluded. Some studies also used diuretics or sodium restriction. Eligible studies were those of patients with microalbuminuria and proteinuria of diabetic and other causes which measured albuminuria or proteinuria using timed quantitative measurements of spot urine specimens. Studies of patients with renal transplants or normal urinary protein excretion were excluded. In the included studies, the average age of the patients ranged from 11 to 64 years and the average follow-up period ranged from 1 to 12 months.

Two reviewers independently screened studies for eligibility, with any disagreements resolved by consensus or referral to another reviewer.

Assessment of study quality
Study quality was assessed using the following criteria: design (parallel or crossover); allocation concealment; blinding (patients and caregivers); use of intention-to-treat (ITT) or per-protocol (PP) analysis; and the reporting of withdrawals and drop-outs. In addition, for crossover trials the duration of the washout period and reporting of carryover effects were assessed.

Three authors performed the quality assessment, with any disagreements resolved by consensus or referral to a fourth reviewer.

Data extraction
The primary outcome was calculated as the ratio of the mean final level of proteinuria for the intervention group compared with the control group. Studies already reporting log-transformed ratios of effect had data extracted directly, regardless of whether the analysis was adjusted for covariates or not. For studies reporting outcomes in other forms (i.e. median, percentage change) transformations were used. Data from crossover trials were extracted on the assumption that there was no carryover effect (i.e. the results from both periods were independent).

Three reviewers independently extracted the data, with any disagreements resolved by consensus or referral to a fourth reviewer.
reviewer. If a study had two or more doses of the same drug, the group with the highest dose was included.

**Methods of synthesis**
The data were combined in a meta-analysis using a random-effects model. As the log-transformed data were pooled, the pooled results were then transformed back to the original measurement scale. Separate analyses were performed for short-term outcomes (1 to 4 months’ follow-up) and longer-term outcomes (5 to 12 months’ follow-up). Funnel plots were used to evaluate publication bias. Statistical heterogeneity was assessed using the $I^2$ statistic. Subgroup analyses were also used to explore possible reasons for heterogeneity: severity of baseline protein excretion (microalbuminuria (20 to 200 mg/g or 30 to 300 mg/day creatinine) compared with proteinuria (over 300 mg/day albumin or over 500 mg protein per day or per gram of creatinine); cause of renal disease (diabetic compared with non-diabetic); study design (parallel-group compared with crossover); allocation concealment; blinding; analysis (ITT compared with PP). Studies with similar treatment effects and drug actions were combined in the subgroup analyses.

**Results of the review**
Forty-nine RCTs were included: 12 compared ARBs with placebo (n=3,551); 9 compared ARBs with calcium-channel blockers (n=1,892); 23 compared ARBs with ACE inhibitors (n=1,301); 16 compared combination therapy (ARB plus ACE inhibitors) with ARBs (n=571); and 23 compared combination therapy with ACE inhibitors (n=711). Some studies contained more than one treatment comparison. The quality of the studies varied: 7 studies met all three quality criteria (allocation concealment, blinding and ITT analysis), 15 met two, 12 met one and 15 met none. For crossover studies, all but 3 studies reported a prolonged washout period or no statistically significant carryover effects.

**ARB monotherapy.**
For outcomes up to 4 months, ARBs achieved significantly lower proteinuria levels compared with placebo (means ratio 0.57, 95% confidence interval, CI: 0.47, 0.68; based on 8 comparisons) and calcium-channel blockers (means ratio 0.69, 95% CI: 0.62, 0.77; based on 7 comparisons), but there was no evidence of a difference in comparison with ACE inhibitors. For outcomes between 5 and 12 months, ARBs achieved significantly lower proteinuria levels compared with placebo (means ratio 0.66, 95% CI: 0.63, 0.69; based on 6 comparisons) and calcium-channel blockers (means ratio 0.62, 95% CI: 0.55, 0.70; based on 5 comparisons), but there was no evidence of a difference in comparison with ACE inhibitors.

**Combined ARB and ACE inhibitor therapy.**
For outcomes up to 4 months, combination therapy achieved significantly lower proteinuria levels compared with ARB alone (means ratio 0.76, 95% CI: 0.68, 0.85; based on 14 comparisons) and ACE inhibitors alone (means ratio 0.78, 95% CI: 0.72, 0.84; based on 21 comparisons). For outcomes between 5 and 12 months, combination therapy achieved significantly lower proteinuria levels compared with ARB alone (means ratio 0.75, 95% CI: 0.61, 0.92; based on 7 comparisons) and reduced levels compared with ACE inhibitors alone, although this result was not statistically significant.

Only the comparison of ARB with placebo for short-term outcomes showed substantial heterogeneity ($I^2=86\%$). Subgroup analyses of clinical characteristics did not show any possible reasons for this heterogeneity. However, larger treatment effects were seen in studies that did report allocation concealment compared with those that did not (p=0.016), and in crossover compared with parallel-group studies (p=0.02); these results were consistent for the monotherapy and combination therapy analyses. Larger treatment effects were also seen in the blinded studies compared with non-blinded studies (p=0.04) for the combination therapy analyses. There was no evidence of publication bias.

**Authors’ conclusions**
ARBs reduce proteinuria, regardless of the underlying disease and the amount of proteinuria. ARBs are more effective at reducing proteinuria than placebo or calcium-channel blockers, but have a similar effect size to ACE inhibitors. The combination of ARBs and ACE inhibitors is more effective than either drug alone, but uncertainty concerning adverse events and outcomes important to patients limit the clinical applicability of these findings.
CRD commentary
This review had clearly stated inclusion criteria, specifying details of the interventions, participants, study designs and outcomes. The methods, including details of how the studies were selected, quality assessed and data extracted, were reported clearly. Every aspect was performed by a number of authors independently, which helps prevent errors in the review process. One major database and a register of controlled trials were searched for studies, and additional efforts made by screening reference lists and contacting experts. However, the restriction to only English language studies may mean that some relevant studies were missed. The studies were quality assessed using questions relevant to RCTs, and issues of study quality were discussed in relation to the review's conclusions. The statistical analysis methods were described clearly and appear appropriate, and sources of between-study heterogeneity were explored. The conduct and reporting of this review were good, and its conclusions appear reliable, although the inclusion of only studies published in English might have introduced some language bias.

Implications of the review for practice and research
Practice: The authors stated that patients for whom ARB or ACE inhibitor therapy fails to reduce proteinuria to less than 0.5 g/day should be started on antiproteinuric therapy and monitored closely for proteinuria reduction, serum potassium levels and adverse events.

Research: The authors stated that as proteinuria is a surrogate outcome, further research assessing outcomes that are important to patients is needed. A long-term RCT of combination therapy compared with either ARB or ACE inhibitor monotherapy in patients with proteinuria representative of those seen in clinical practice, assessing end-stage renal diseases and the effect of different proteinuria levels on renal disease progression, and reporting adverse events, is needed.

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Other publications of related interest
This additional published commentary may also be of interest.


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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.