ACEI/ARB therapy for IgA nephropathy: a meta analysis of randomised controlled trials
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CRD summary
The authors concluded that angiotensin converting-enzyme inhibitor/angiotensin II receptor blocker agents appeared to improve proteinuria and have a protecting effect on renal function. Given potential sources of bias that included methodological variability, inclusion of studies with small samples sizes and use concomitant medication by participants, the authors’ conclusions should be treated with caution.

Authors’ objectives
To evaluate the effects of angiotensin converting-enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) on immunoglobulin A nephropathy (IgAN)

Searching
MEDLINE (1966 to 2008), EMBASE (1988 to 2008) and Cochrane Central Register of Controlled Trials (CENTRAL) specialised renal registry were searched. Search terms were reported. Nephrology journals were handsearched and reference lists of retrieved articles were checked for additional studies.

Study selection
Randomised controlled trials (RCTs) that compared ACEIs and/or ARBs with various comparators (placebo, other anti-hypertensive agents and/or non-immunosuppressive agents) in patients with IgAN were eligible for inclusion. There was no restriction on dose or type of ACEI/ARB. Studies with immunosuppressants in only one arm were excluded. Outcomes of interest included proportion of patients whose renal function had deteriorated (defined as renal impairment reaching end stage renal disease or requiring dialysys therapy or transplantation), frequency of adverse effects and changes in glomerular filtration rates (GFR) and proteinuria.

The treatment group consisted of either an ACEI (fosinopril, enalapril, benazepril, temocapril, trandolapril, ramipril or captopril) or an ARB (losartan or valsartan) or a combination of both treatments. The control group varied and included calcium-channel blockers (nifedipine and amlodipine), a beta-blocker (nadolol), conventional treatment and placebo (or no treatment). Most studies included patients who received concomitant drugs such as beta-blockers, calcium-channel blockers and thiazide diuretics. Follow-up duration was between three and 78 months. Participants’ age (where stated) ranged from nine to 74 years. Most patients had proteinuria (>1g/24 hours).

Two reviewers independently performed study selection. The authors did not state how discrepancies were resolved.

Assessment of study quality
Study quality was evaluated with the five-item Jadad scale of blinding, randomisation and withdrawals with a possible maximum of 5 points for each study. Studies with a score below 3 werees rated as poor quality. The authors assessed studies for evidence of allocation concealment and intention-to-treat (ITT) analysis.

Two reviewers independently assessed study quality. The authors did not state how disagreements were resolved.

Data extraction
Data were extracted to calculate risk ratios (RR) for deterioration in renal function and adverse effects and mean differences for proteinuria, with 95% confidence intervals (CI).

Two reviewers independently extracted data. Primary authors were contacted for additional information. The authors did not state how disagreements were resolved.

Methods of synthesis
A fixed-effect model with Mantel-Haenszel weights was used to produce pooled risk ratios and weighted mean differences (WMD). Where there was evidence of statistical heterogeneity, the DerSimonian and Laird random-effects model was applied. Statistical heterogeneity was assessed using the \( \chi^2 \) test \((p<0.05)\). Evidence for publication bias was explored graphically with funnel plots and statistically with Begg's test. Fixed-effect meta-regression was undertaken to assess whether there was a difference between the two treatment groups in the effect of variables (age, baseline creatinine clearance, systolic and diastolic blood pressures) on outcomes.

Sensitivity analyses were performed to evaluate differences in pooled results by comparison of the random-effects model with the fixed-effect model. To assess the effect of study quality on the results, pooled estimates were recalculated with the exclusion of poor-quality studies (Jadad score <3).

**Results of the review**

Eleven RCTs \((n=624 \text{ patients, calculated from tables})\) were included. Five studies scored 3 or more on the quality assessment, three studies scored 2 and three studies scored 1.

**Renal function (eight RCTs, \(n=461 \text{ patients}\))**: Treatment with ACEIs/ARBs had a superior benefit over controls in preserving renal function \((OR 0.29, 95\% \text{ CI 0.17 to 0.49 from forest plot})\). Discrepancies were noted between figures reported in the text \((reported \text{ as RR})\) and those from the forest plot.

**Daily proteinuria (seven RCTs, \(n=463 \text{ patients}\))**: ACEIs/ARBs were associated with a statistically significant reduction in proteinuria compared with controls \((\text{WMD } -0.67, 95\% \text{ CI } -0.85 \text{ to } -0.49)\).

**Adverse effects (three RCTs, \(n=219 \text{ patients}\))**: There were no significant differences in any adverse effect between the groups.

**Patient characteristics**: Fixed-effect meta-regression found no significant differences between treatment groups in age or creatinine clearance at baseline. Reductions in systolic and diastolic blood pressures were similar between the treatment groups. There was no evidence of statistical heterogeneity.

**Sensitivity analyses**: Model choice \((\text{random-effects or fixed-effect})\) or study quality did not influence the results.

Results from funnel plots and Begg's test showed no evidence of publication bias.

**Authors' conclusions**
The authors concluded that ACEIs/ARBs appeared to have a protective effect on renal function and improved proteinuria in patients with IgAN.

**CRD commentary**
The review question was clearly stated with respect to participants, interventions, study design and outcomes. Relevant databases were searched for published studies in any language. There was little effort to retrieve unpublished studies though evidence of publication bias was not found to be present when investigated. Results of the study quality assessment indicated that more than half of the included studies were of poor quality, although inclusion of such studies did not appear to have a major impact on the overall results. The authors minimised the potential for errors by performing tasks in duplicate; it was unclear how they sought to resolve any disagreements. Appropriate statistical methods were used in pooling results. Statistical heterogeneity was explored and not found to be present. Meta-regression methods were poorly described and it was questionable whether it was applied appropriately. Other potential sources of bias that included variable lengths of follow-up time, variability among interventions and use concomitant medication \((\text{detailed information not provided})\) were identified as limitations by the authors, but it did not appear that these were accounted for in the conclusions.

Methodological variability, inclusion of studies with small sample sizes and use of concomitant medication were potential sources of bias in this review. Although the conclusions were consistent with the results presented, they should be regarded with caution given the limitations highlighted.
Implications of the review for practice and research

Practice: The authors stated that current evidence-based practice guidelines should continue to emphasise ACEI/ARB agents as the primary pharmacological therapy for patients with IgAN.

Research: The authors stated that use of ACEI/ARB agents was a promising strategy and should be investigated further. Studies that used ACEI/ARB agents alone without concomitant drugs were needed.

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