Renin angiotensin system blockade in kidney transplantation: a systematic review of the evidence

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CRD summary
This review evaluated the effect of angiotensin-converting enzyme-inhibitor or angiotensin receptor blocker use following kidney transplantation. The authors found that treatment with an angiotensin-converting enzyme-inhibitor or angiotensin receptor blocker produced clinically conflicting results of reductions in proteinuria, haematocrit and glomerular filtration rate in renal transplant recipients. These conclusions seemed sufficiently cautious.

Authors' objectives
To evaluate the effect of angiotensin-converting enzyme-inhibitor or angiotensin receptor blocker use following kidney transplantation.

Searching
MEDLINE (1966 to February 2007), EMBASE (1980 to February 2007) and the Cochrane Central Register of Controlled Trials (fourth quarter, 2006) were searched for studies published in any language. Search terms were not reported but were available from the authors. Bibliographies of the included studies were also searched for eligible studies and experts in the field were consulted.

Study selection
Randomised controlled trials (RCTs) of adult patients receiving primary or repeat renal transplant (deceased or living donor), who were randomised to be treated with either an angiotensin-converting enzyme-inhibitor or angiotensin receptor blocker compared with active medication, placebo or usual care, were eligible for inclusion. Trials that involved dual-organ transplants were excluded. Parallel and crossover RCTs that evaluated patients three days to more than six months since transplantation, with follow-up ranging from two days to 60 months were included.

Trials had to report one or more of the following outcomes: serum creatinine, creatinine clearance, glomerular filtration rate, blood pressure, proteinuria, haemoglobin, haematocrit, potassium, allograft survival or patient survival. If several articles of the same trial were found, the report that presented long-term data was included in the primary analysis.

The primary outcome measure was change in renal function (creatinine, creatinine clearance or glomerular filtration rate). Secondary outcomes included change in blood pressure, haemoglobin or haematocrit, proteinuria, and potassium concentration. The method of measuring/estimating glomerular filtration rate varied in the included trials.

The patients included in the primary trials fulfilled a variety of inclusion criteria for blood pressure, type of transplant, erythrocytosis and creatinine. The included interventions were benazapril, candesartan, captopril, enalapril, fosinopril, lisinopril, losartan, perindopril, quinapril, trandolapril and valsartan. The controls included standard care, placebo, amlodipine, atenolol, nifedipine and theophylline.

Two reviewers independently selected primary studies and disagreements were resolved by consensus.

Assessment of study quality
Methodological quality of primary studies was assessed using the Jadad scale, which evaluates blinding, randomisation, withdrawals and dropouts to give a quality score out of 5.

The authors did not state how the validity assessment was performed.

Data extraction
Data were extracted on allograft survival and patient survival and the continuous outcomes (recorded as change from baseline) serum creatinine, creatinine clearance, glomerular filtration rate, blood pressure, proteinuria, haemoglobin,
haematocrit and potassium.

Data were extracted independently by two reviewers using a standardised form.

**Methods of synthesis**

Weighted mean differences and corresponding 95% confidence intervals were pooled in fixed-effect and random-effects DerSimonian and Laird models. Intention-to-treat analyses were included. Statistical heterogeneity was assessed using the Q-statistic. Meta-regression was also performed in order to determine the effect of baseline glomerular filtration rate, time post-transplantation and length of study follow-up on the difference in change in glomerular filtration rate between treatment groups. Mixed models were used to pool treatment effect across trials, controlling for mean baseline glomerular filtration rate, time post-transplantation, study length and compared to the standard pooled results.

**Results of the review**

Twenty-one randomised controlled trials (RCTs) were included (n=1,549 patients); 14 parallel trials (n=1,419) and seven crossover trials (n=130). Trial size ranged from nine to 502. The majority of trials had less than 100 participants. Allocation concealment was adequate in five trials. Six trials were reported to be double blind. No statistically significant heterogeneity was indicated.

**Glomerular filtration rate:** Angiotensin receptor blocker/angiotensin-converting enzyme-inhibitor use was associated with a significantly lower change in glomerular filtration rate compared with control (weighted mean difference -5.7 ml/min, 95% confidence interval (CI): -8.7 to -2.8; p<0.001, 12 RCTs). The results were similar for parallel studies with at least 12 months follow-up (four RCTs). Baseline glomerular filtration rate, duration of follow-up and time post-transplantation were not significantly associated with the change in glomerular filtration rate in the meta-regression analysis. Sensitivity analyses found that overall magnitude and direction of effect size was consistent across all subgroups studied.

**Haematocrit:** Angiotensin-converting enzyme-inhibitor/angiotensin receptor blocker use was associated with a statistically significant decrease in change in haematocrit (weighted mean difference -4.3%, 95% CI: -6.4 to -2.2; p<0.001, eight RCTs). Results for parallel studies with at least 12 months follow-up were similar (three studies).

**Potassium:** Angiotensin-converting enzyme-inhibitor/angiotensin receptor blocker use was associated with a statistically significant increase in change in potassium (weighted mean difference 0.19mmol/L, 95% CI: 0.09 to 0.28; p=0.006, nine RCTs). Results for parallel studies with at least 12 months follow-up did not significantly increase change in potassium compared with control when restricted to this study design (three RCTs).

**Proteinuria and mean arterial pressure:** Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use was not significantly associated with change in proteinuria (four RCTs) or change in mean arterial pressure (14 RCTs). However, when the studies of proteinuria were restricted to parallel studies with at least 12 months follow-up, the change in proteinuria was significantly greater in the angiotensin-converting enzyme-inhibitor/angiotensin receptor blocker group compared with control (weighted mean difference -0.47gm/day, 95% CI: -0.86 to -0.08; p=0.02, two RCTs).

One trial compared candesartan with placebo to evaluate patient or graft survival but was discontinued prematurely when interim analysis found that the outcome rate was only 25% of what was expected.

**Authors' conclusions**

Treatment with an angiotensin-converting enzyme-inhibitor or angiotensin receptor blocker produced clinically conflicting results of important reductions in proteinuria, haematocrit and glomerular filtration rate in renal transplant recipients. There were insufficient data to determine the effect of angiotensin-converting enzyme-inhibitor or angiotensin receptor blocker use on patient or graft survival.

**CRD commentary**

The research question was clear with supporting inclusion criteria for participants, intervention, outcomes and study...
design. The authors searched for studies published in any language, reducing the possibility of language bias. However, no attempts to identify unpublished studies were reported which increased the risk of publication bias. Study selection and data extraction were performed independently by two reviewers, which minimised the risk of bias and error in these processes. Details of how validity assessment was performed were not reported, so it is not known whether the authors took similar steps in this process. The authors assessed statistical heterogeneity and study quality and took the findings into consideration in their interpretation of results. The primary trials varied in follow-up duration, sample size and time taken to start angiotensin-converting enzyme-inhibitor/angiotensin receptor blocker, which may limit the strength and generalisability of the conclusions. There were some limitations due to the primary trials and review methods, but the authors conclusions seem sufficiently cautious.

Implications of the review for practice and research
Practice: The authors stated that the review provided quantitative estimates of the risks and benefits of angiotensin-converting enzyme-inhibitor or angiotensin receptor blocker use that can be used by clinicians considering prescribing these medications to kidney transplant recipients.

Research: The authors stated that an adequately powered RCT of sufficient duration, that examines meaningful outcomes such as patient or allograft survival, is necessary to address whether angiotensin-converting enzyme-inhibitor or angiotensin receptor blocker use is beneficial in the kidney transplant population.

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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.