Combination therapy with an angiotensin receptor blocker and an ACE inhibitor in proteinuric renal disease: a systematic review of the efficacy and safety data

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CRD summary
The authors concluded that the combination of an angiotensin-converting enzyme inhibitor and an angiotensin receptor blocker was associated with a short-term decrease in proteinuria in adults with chronic proteinuric renal disease, and appeared safe. Overall, this was a well-conducted review and the authors’ conclusions are likely to be reliable.

Authors' objectives
To determine the efficacy of combination therapy with an angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) in patients with chronic proteinuric renal disease.

Searching
MEDLINE (1966 to January 2006), EMBASE (1980 to 2004) and the Cochrane Library (Issue 1, 2006) were searched for relevant papers published in the English language; the search terms were reported. The authors also checked the reference lists of included studies, the reviewers' personal files and references suggested by local experts.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials were eligible for inclusion; parallel-group trials and crossover trials were included in the review.

Specific interventions included in the review
Studies that compared an ARB in combination with an ACE inhibitor with an ACE inhibitor alone were eligible for inclusion. Studies in which the duration of treatment was less than 4 weeks were excluded. The ACE inhibitors included in the studies were trandolapril, benazepril, lisinopril, enalapril, temocapril, fosinopril and ramipril. The ARBs included in the review were losartan, valsartan, candesartan and irbesartan. The duration of treatment ranged from 4 to 16 weeks in the crossover trials, and from 3 months to 2.9 years (median) in the parallel-group trials.

Participants included in the review
Studies of adult patients with diabetic or non-diabetic chronic proteinuric renal disease (defined as proteinuria with protein >300 mg/day) were eligible for inclusion. Studies that included renal transplant recipients were excluded.

Outcomes assessed in the review
The primary outcomes of interest were changes in 24-hour proteinuria, serum potassium level and glomerular filtration rate (GFR) after addition of an ARB to pre-existing ACE-inhibitor therapy. The secondary outcomes included change in blood-pressure (BP), progression to end-stage renal disease, and death.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected papers for inclusion in the review. Any differences were resolved by consensus.

Assessment of study quality
The validity of the primary studies was assessed using the Jadad scale, which evaluates reported randomisation, blinding, and withdrawals and drop-outs; the maximum possible score was five. Two reviewers independently evaluated the methodological quality of the primary studies.
Data extraction
Two reviewers independently extracted the data from the primary studies. Any differences were resolved by consensus. The mean and standard deviation were extracted for each outcome of interest. If data were presented for subgroups (patients with and without diabetes), data for each subgroup were entered as two separate studies. Data from ARB monotherapy arms were not extracted. Weighted mean differences (WMDs) were calculated for continuous outcomes. Reported 95% confidence intervals (CIs) or interquartile ranges of skewed proteinuria data were converted to standard deviations.

Methods of synthesis
How were the studies combined?
The crossover trials were combined in a meta-analysis using a fixed-effect model (in the absence of statistical heterogeneity) or a random-effects model (when there was evidence of statistical heterogeneity). Summary estimates for the outcomes of interest were presented as WMDs with 95% CIs. Parallel-group trials were combined in a narrative.

How were differences between studies investigated?
The Cochran Q statistic was used to assess statistical heterogeneity; a p-value of less than 0.10 was considered significant. A subgroup analysis was performed for studies that predominantly included patients with diabetic nephropathy, or studies that involved nondiabetic proteinuric chronic kidney disease (CKD).

Results of the review
Twenty-one studies (n=654) were included: 5 parallel-group trials (n=281) and 16 crossover trials (n=373).

Crossover trials (16 randomised controlled trials).

Five studies included patients with non-diabetic renal disease, 7 studies included diabetic patients, and 4 studies included patients with both diabetic and non-diabetic renal disease. The Jadad scores for these trials were considered to be moderate to high (median score 3.5); 4 studies were deemed to be of a low quality. All studies were short term (range: 4 to 16 weeks).

When all 16 studies were pooled, a significant decrease in proteinuria was found with combination therapy compared with ACE inhibitor alone (WMD 440 mg/day, 95% CI: 289, 591); statistically significant heterogeneity was found (Q=84.9, p<0.01). A significant reduction in proteinuria was also found when only studies that predominantly included patients with diabetic nephropathy or non-diabetic proteinuric CKD were pooled; statistically significant heterogeneity was found in both analyses.

Significant decreases in systolic BP (WMD 4.5 mmHg, 95% CI: 2.7, 6.4) and diastolic BP (WMD 2.5 mmHg, 95% CI: 1.6, 3.5) were found in favour of combination therapy when 14 studies were pooled; statistically significant heterogeneity was found (Q=46.7, p<0.01 and Q=28.2, p<0.01, respectively). A significant reduction in BP was found when only studies that predominantly included patients with diabetic nephropathy or non-diabetic proteinuric CKD were pooled; significant heterogeneity was not found for studies involving diastolic BP in non-diabetic proteinuric CKD.

A small but statistically significant decrease in serum potassium level was found in favour of combination therapy when 14 studies were pooled (WMD 0.11 mEq/L, 95% CI: 0.05, 0.17); significant heterogeneity was found (Q=34.7, p<0.01). A decrease in GFR was found with combination therapy compared with ACE inhibitors alone (WMD -1.4 mL/minute, 95% CI: -2.6, 0.2), but this was not statistically significant; no significant heterogeneity was found.

Parallel-group trials.

One study (n=263) found a significant percentage decrease in proteinuria in patients receiving combination therapy compared with immunotherapy (-75.6% versus -44.3%, p=0.01) at the 3-year follow-up; patients receiving combination therapy also demonstrated a significant decrease in serum creatinine level or end-stage renal disease compared with ACE-inhibitor therapy alone (11.5 versus 23%, p=0.018), but no significant difference was found between treatment groups for BP.
One study (n=36) found a significant decrease in mean protein excretion in the combination group compared with ACE-inhibitor monotherapy after 6 months, but no significant difference was found between treatment groups in BP, serum potassium levels or creatinine clearance.

One study (n=30) reported a decrease in proteinuria at the 2-month follow-up, but no significant difference was found at the 6-month follow-up and there were no significant between-group differences for BP or GFR.

One study (n=32) found no significant differences between treatment groups for proteinuria or systolic BP, although a significant decrease in diastolic BP was found in favour of combination therapy compared with enalapril monotherapy at the 3-month follow-up. A short-term decrease in creatinine clearance was also reported in the enalapril group.

One study (n=21) reported a greater decrease in proteinuria with combination therapy compared with temocapril monotherapy at the 6-month follow-up. No change from baseline was shown in GFR or serum potassium level. BP was found to decrease in the combination therapy group but not the temocapril group.

Authors' conclusions
The combination of ACE inhibitor and ARB therapy in adults with chronic proteinuric renal disease was associated with a decrease in proteinuria in the short term. Combination therapy was safe, without clinically meaningful changes in serum potassium levels or GFRs.

CRD commentary
The review question was supported by clear inclusion criteria, and several sources were searched for relevant papers. Limiting the search to papers published in English raises the possibility of publication bias, which the authors made no attempt to assess. Methods were used to minimise reviewer errors and bias in the study selection, quality assessment and data extraction processes. The methodological quality of the included studies was assessed and the results reported. The analysis was appropriate; heterogeneity was assessed and the authors investigated possible sources of it. Significant heterogeneity was found for most analyses, suggesting that the size of the treatment effect differed across studies. Overall, this was a well-conducted review and the authors' conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors recommended combination therapy for the preservation of renal function in patients with proteinuric CKD.

Research: The authors stated that trials with longer follow-up are needed to determine whether a decrease in proteinuria would result in significant preservation of renal function.

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