Combination therapy with an ACE inhibitor and an angiotensin receptor blocker for diabetic nephropathy: a meta-analysis

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CRD summary
The authors concluded that short-term combination therapy with an angiotensin-converting enzyme inhibitor (ACEI) and an angiotensin-receptor blocker is more effective than ACEI alone for diabetic nephropathy. Weaknesses identified in the review methodology and differences amongst the included studies mean that the reliability of the authors' conclusions is unclear.

Authors' objectives
To evaluate the effectiveness of combination therapy using an angiotensin-converting enzyme inhibitor (ACEI) and an angiotensin-receptor blocker (ARB) for diabetic nephropathy (DN).

Searching
MEDLINE (January 1966 to May 2006), EMBASE (1980 to May 2006), CINAHL (1982 to May 2006) and the Cochrane Database of Systematic Reviews (no dates given) were searched for relevant studies; the search terms were reported. Only studies published in English were eligible for inclusion. Additional studies were sought using references from original manuscripts and review articles.

Study selection
Randomised, controlled, parallel or crossover trials of an ACEI and ARB as a combination treatment for DN, compared with either regimen as monotherapy, were eligible for inclusion. The primary outcome of interest was 24-hour urinary protein excretion. Secondary outcomes were the percentage reductions in protein excretion, blood-pressure, serum creatinine, serum potassium and glomerular filtration rate (GFR), to assess the safety of dual blockage of the renin-angiotensin-aldosterone system (RAAS). The included studies were between 8 and 12 weeks’ duration, and evaluated patients with type 1 or type 2 diabetes mellitus, proteinuria or hypertension. Various combinations and doses of irbesartan, lisinopril, enalapril, captopril, valsartan, benazepril, candesartan, ramipril, temocapril, losartan, fosinopril and imidapril were compared with placebo and/or one of the active treatments.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Data were extracted on each outcome, ultimately to calculate the weighted mean difference (WMD) and 95% confidence interval (CI).

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
The WMDs were pooled in a meta-analysis using a random-effects model (DerSimonian and Laird). Statistical heterogeneity was assessed using the $\chi^2$ test. Clinical heterogeneity was assessed in subgroup analyses, largely to explore the impact of excluding non-randomised and unblinded studies. The potential for publication bias was reported to have been assessed using funnel plots.

Results of the review
Ten randomised controlled trials (n=169) were included in the review, of which nine had a crossover design.
No results were presented in relation to publication bias, but the authors stated that bias could not be ruled out.

The pooled results from 10 trials indicated a significant reduction in 24-hour proteinuria using combination therapy (ACEI and ARB) compared with ACEI alone (WMD -177, 95% CI: -319, -35, p=0.01). There was statistically significant heterogeneity between the trials (p≤0.005). A subgroup analysis of 8 trials showed there to be a significant benefit from the use of submaximal doses of ACEI (p=0.03). A further analysis of 5 trials suggested a significant correlation between lower baseline levels of proteinuria and declining benefits of combination therapy (p<0.03). The authors reported that there was little or no impact of excluding short-term or less methodologically robust studies from the review, although heterogeneity was no longer significant.

In terms of safety outcomes arising from combination therapy, the analysis of 7 trials showed mean changes in systolic and diastolic blood-pressure were significantly reduced by 5.2 mmHg (95% CI: -8.4, -2.1, p<0.01) and 5.3 mmHg (95% CI: -8.4, -2.2, p<0.01), respectively. Dual blockade of the RAAS showed a significantly decreased GFR of 3.87mL/minute (95% CI: 7.32, 0.42, p=0.03) and serum potassium was significantly increased by 0.2 mmol/L (95% CI: 0.08, 0.32, p<0.01).

Authors' conclusions
In the short term, combination therapy with ACEI and ARB reduces 24-hour proteinuria to a greater extent than ACEI alone. The benefit also yields small effects on GFR, serum creatinine, potassium and blood-pressure.

CRD commentary
The review question was clear and appropriate inclusion criteria were reported for the interventions, outcomes and study designs. Relevant sources were searched to identify studies, but the restriction to studies reported in English and no apparent search for unpublished material may mean that relevant studies were missed and language and publication biases introduced. Publication bias was reported to have been assessed, the results were not available for judgement to be made. The absence of any reported review methods means that the potential for error and bias cannot be ruled out. The lack of a formal validity assessment also contributes to the potential unreliability of the included studies and their synthesis. Although there was some analysis of heterogeneity, the decision to pool studies with different characteristics and small sample sizes represents a further potential limitation of this review. Given the several methodological shortcomings highlighted, the reliability of the authors' conclusions is unclear.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that future studies should employ accepted clinical end points (doubling of serum creatinine, onset of end-stage renal disease), establish the long-terms benefits of combination therapy, define the optimal dose of each drug, and test optimal doses of monotherapy against combination therapy. The role of blood-pressure in the effectiveness of combination therapy is a further area of potential interest.

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