Antiproteinuric effect of blood-pressure-lowering agents: a meta-analysis of comparative trials

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Authors’ objectives
To evaluate the effectiveness of angiotensin-converting enzyme (ACE) inhibitors in lowering proteinuria, and to determine whether diabetic and non-diabetic patients differ in their antiproteinuric response to blood-pressure reduction.

Searching
MEDLINE and EMBASE were searched up to February 1994 (start date not given) using the following search terms: for MEDLINE, the subject headings were ‘angiotensin-converting enzyme inhibitors’ combined with ‘calcium-channel blockers’, ‘adrenergic beta receptors blockers’, ‘diuretics’, ‘adrenergic alpha-receptors blockers’, ‘adrenergic alpha receptor agonists’ or ‘pyridazines’; and for EMBASE, ‘dipeptidyl carboxypeptidase inhibitor’ combined with ‘calcium antagonist’, ‘beta adrenergic receptor blocking agent’, ‘diuretic agent’, ‘alpha adrenergic receptor blocking agent’, ‘alpha adrenergic receptor stimulating agent’ or ‘peripheral vasodilating agent’. These were then combined with the terms ‘human’ (EMBASE:888) and either ‘proteinuria’ or ‘nephrotic syndrome’.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), non-randomised comparative (parallel) studies, randomised crossover trials and longitudinal studies were included.

Specific interventions included in the review
Enalapril (in doses ranging across studies from 5-40 mg/day), atenolol (25-100 mg/day), nicardipine (60-120 mg/day), lisinopril (2.5-80 mg/day), diltiazem (196 mg/day), verapamil(120-2,450 mg/day), nitrendipine (10-40 mg/day), captopril (12.5-100 mg/day), dilevaloi (200 mg/day), ramipril (5 mg/day), felodipine (8 mg/day), doxazosin (2 mg/day), cilazapril (1.25-2.5 mg/day), indapamide (2.5 mg/day), alpha-methyldopa (781 mg/day), benazepril (20 mg/day), metoprolol (50-200 mg/day), chlorthalidone (12.5 mg/day), perindopril (2-8 mg/day), nifedipine (5-80 mg/day), prazosin (8 mg/day), and various other beta-blockers and diuretics. Combinations examined include frusemide-atenolol, nifedipine(20 mg/day)-nicardipine(8 mg/day), metoprolol(200 mg/day)-chlorothiazide(25 mg/day), metoprolol(100-200 mg/day)-hydrochlorothiazide(25-50 mg/day), captopril-enalapril, nifedipine-amlopidine-nitrendipine and hydrochlorothiazide-guanfacine.

Participants included in the review
Patients with renal disease with and without diabetes were included. Studies performed in patients with heart failure, renal transplantation or renovascular hypertension were excluded.

Outcomes assessed in the review
Urinary albumin excretion (mg/day), level of proteinuria (g/day), mean arterial pressure (mmHg) and glomerular filtration rate (GFR) (ml/min). For each study the treatment effect was defined as [1 minus (treatment divided by the baseline)] multiplied by 100.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The study designs of the included studies were used as an indicator of the quality of the study. This was done by determining the independent effects of various aspects of study design (randomised versus non-randomised, blinded...
versus non-blinded, parallel versus crossover design) on the outcome in a stepwise multiple regression. The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
The overall mean treatment effect with 95% confidence interval (CI) was calculated. The results of individual studies were weighted by the number of included patients and the inverse of the variance.

How were differences between studies investigated?
Sources of heterogeneity were investigated by examining subgroups using separate analyses for different classes of antihypertensive medication (ACE inhibitors, calcium-channel blockers and beta-blockers) and different patients groups (diabetic and non-diabetic patients). The multiple regression analysis was performed separately for randomised versus non-randomised blinded versus non-blinded studies, and crossover versus parallel design studies.

Results of the review
Forty-one studies were included: 23 of parallel, 15 of crossover and 3 of longitudinal design. The total number of patients was 1,124 (558 non-diabetic, 566 diabetic).

Main results: the mean anti-proteinuric effect of ACE inhibitors was significantly greater than that of other antihypertensive drugs. -39% (95% CI: -42.8, -36.8) versus -17% (95% CI: -19.1, -15.1%), respectively; difference 24% (95% CI: 19.5, 28.6%). The blood-pressure lowering effect was similar at -12% (95% CI: -12.8, -11.2%) versus -11.4% (95% CI: -11.7, -11.1%), respectively; difference -0.8% (95% CI: -1.8, 0.2%). ACE inhibitors induced a similar response in diabetic and non-diabetic patients: -37.4% (95% CI: -41.3, -33.2) versus -43.7% (95% CI: -48.1, -39%). The fall in blood-pressure with ACE inhibitors was also similar in both groups: -12.4% (95% CI: -13.9, -11.0%) versus -11.8% (95% CI: -12.7, -10.8%). However, with the comparator drugs, urinary protein excretion was greater in diabetic patients: -23.7% (95% CI: -26.5, -20.8%) versus -12.3% (95% CI: -14.9, -9.6%). The fall in blood-pressure was also different between both groups: in diabetic patients, mean arterial blood-pressure decreased by 14% (95% CI: -14.6%, -13.5%) compared to a drop of 10.6% (95% CI: -10.9% versus -10.3%) in non-diabetics.

Results of the multiple regression model using weighting by sample size: the variables with best fit were (in order of importance): class of medication (p<0.001), change in mean arterial blood-pressure (p<0.001), baseline GFR (p<0.001) and presence/absence of diabetic neuropathy (p=0.02). The greatest reduction in urinary protein and albumin excretion occurred in patients treated with ACE inhibitors. Calcium-channel antagonists and beta-blockers showed a poor response.

Authors' conclusions
ACE inhibitors lower urinary protein excretion significantly more than other antihypertensive agents with similar blood pressure-lowering effects. Non-ACE inhibitors decrease urinary protein excretion to a greater extent in diabetic patients. However, the fall in blood-pressure is also more marked.

CRD commentary
There are two main criticisms relating to this review. One concerns the pooling of studies of differing designs: pooling of the crossover trials and RCTs may underestimate the size of the effect, given the large proportion of crossover trials involved. The second concerns the assessment of the quality of the individual studies, which was somewhat limited. Although study design was used as a proxy for study quality, a more thorough examination of study quality would have been useful. Thus, a review using the same studies but with more rigorous inclusion criteria, which includes only high quality RCTs,
may well obtain a different estimate of the true effect size.

**Implications of the review for practice and research**
Further studies are required to determine whether differences in antiproteinuric efficacy between various antihypertensive agents result in differences in renoprotective effect.

**Bibliographic details**

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Subject indexing assigned by NLM

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**Record Status**
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.