Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease: a meta-analysis of patient-level data


Authors' objectives
To examine the efficacy of angiotensin-converting enzyme (ACE) inhibitors for the treatment of nondiabetic renal disease.

Searching
MEDLINE was searched from May 1977 to September 1997 for English language studies. In addition, abstracts in the proceedings of American and international conferences, review articles and references cited in published studies were also checked. The authors contacted investigators in the field about additional published or unpublished studies in the area.

Study selection
Study designs of evaluations included in the review
The review included individual patient data (IPD) from randomised controlled trials (RCTs) with a follow-up of at least one year, which provided data on the outcome measures of interest. The mean duration of follow-up was 2.2 years for both groups (standard deviation 1.1).

Specific interventions included in the review
Studies that compared the efficacy of antihypertensive regimens with and without ACE inhibitors in participants with predominantly nondiabetic renal disease were eligible for inclusion. The actual drugs included in the review were: enalapril, 2.5 to 40 mg/day (7 studies); captopril, 12.5 to 50 mg/day (1 study); benazepril, 10 mg/day (1 study); cilazapril, 2.5 to 5 mg/day (1 study); and ramipril, 1.25 to 5 mg/day (1 study). The comparators were placebo (5 trials), atenolol or acebutolol (3 studies) and nifedipine (2 studies); the control medication was not specified in the remaining study. Other antihypertensive medications were also used in both groups to reach the target blood-pressure (BP) in all studies.

Participants included in the review
Patients with nondiabetic renal disease were eligible for inclusion. The primary studies in the review included patients with glomerular disease, polycystic kidney disease, hypertensive nephrosclerosis and tubulointerstitial disease. Hypertension or decreased renal function was required for entry into all studies. Exclusion criteria common to all studies were acute renal failure, treatment with immunosuppressive medications, clinically significant heart failure, obstructive uropathy, renal artery stenosis, active systemic disease, insulin-dependent diabetes mellitus, history of transplantation, history of allergy to ACE inhibitors and pregnancy.

Outcomes assessed in the review
Two primary outcomes were assessed in the review: end-stage renal disease (ESRD), which was defined as the initiation of long-term dialysis therapy, and the surrogate marker of a two-fold increase in serum creatinine concentration from baseline values. The secondary outcomes assessed were systolic and diastolic BP and urinary protein excretion. Other outcomes included death and a composite outcome of ESRD and death. 'Withdrawal' was defined as the discontinuation of follow-up before the occurrence of an outcome or study end.

How were decisions on the relevance of primary studies made?
The eligibility of the trials for inclusion in the review was verified through contact with the trial investigators.

Assessment of study quality
Five investigators participated in data cleaning. Summary tables were compiled from the IPD from each study and
checked against tables in published and unpublished reports. Any discrepancies were resolved by contacting investigators at the clinical or data coordinating centres wherever possible. As the studies followed different protocols, the variable definitions, follow-up intervals and run-in periods were standardised between the studies. Sixty-six patients with non-insulin dependent diabetes mellitus and 20 patients with missing baseline values for BP, serum creatinine or urinary protein excretion were excluded from the analysis. The authors compared the characteristics of the 1,860 patients included in the analysis with those of the 20 nondiabetic patients who were excluded because of missing values; no significant differences were observed. In addition, the authors checked that all the patient characteristics were balanced between the treatment and control groups at baseline.

**Data extraction**
The data were extracted by any one of five reviewers, and checked against the tables in published and unpublished reports. Data on the year of publication, authors' conclusion, study characteristics, baseline patient characteristics, patient characteristics during follow-up (BP and urinary protein excretion) and the outcomes of interest were tabulated. The study characteristics extracted were sample size, planned duration of follow-up, medication and dosages, concomitant antihypertensive medication use, blinding and dietary advice. The baseline patient characteristics included gender, age, ethnic background, cause of renal disease, BP and urinary protein excretion.

**Methods of synthesis**

How were the studies combined?
A univariate analysis was performed to detect any association between the covariates and outcomes. The baseline patient characteristics were treatment assignment, age, gender, ethnicity, systolic BP, diastolic BP, mean arterial pressure, serum creatinine concentration and urinary protein excretion. The study characteristics were blinding, type of antihypertensive regimen in the control group, planned duration of follow-up, whether dietary protein or sodium were restricted, and the year of publication. The baseline patient characteristics and study characteristics were introduced as fixed covariates. Follow-up patient characteristics (BP and urinary protein excretion) were adjusted as time-dependent covariates. The intention-to-treat principle was followed for comparisons of the randomised groups. Cox proportional hazard regression models were used to determine the effects of assignment to ACE inhibitors and other covariates on the risk of ESRD and the combined outcome.

Multivariate models were built using candidate predictors that were associated with outcome in the univariate analysis; tests were performed for all interactions between covariates and the treatment effect. All P-values were based on two-sided tests, and significance was set at a P-value of less than 0.05. The results were expressed as relative risks (RRs) with 95% confidence intervals (CIs).

How were differences between studies investigated?
A sensitivity analysis was undertaken in which each trial was excluded one at a time. The results between placebo-controlled and active-controlled trials were also explored, as were differences in the time when the baseline measurement was taken.

**Results of the review**

IPD from 11 RCTs were included (total n=1,860); there were 941 patients in the ACE inhibitor group and 919 in the control group.

The mean systolic and diastolic BPs decreased in both groups during follow-up, but these decreases were 4.5 mmHg (95% CI: 3.0, 6.1) and 2.3 mmHg (95% CI: 1.4, 3.2) greater, respectively, in the ACE inhibitor group. The mean urinary protein excretion decreased in the ACE inhibitor group, but remained relatively stable in the control group; the mean decrease in urinary protein excretion was 0.46 g/day (95% CI: 0.33, 0.59) greater in the ACE inhibitor group.

Significantly fewer patients in the ACE inhibitor group than in the control group developed ESRD (7.4% versus 11.6%; P=0.002), the combination end point of doubling of baseline serum creatinine or ESRD (13.2% versus 20.5%; P=0.001), and the combined outcome of ESRD or death (9.6% versus 12.8%; P=0.03). Withdrawal because of nonfatal side-effects (possibly due to ACE inhibitors) and other nonfatal events were more common in the ACE inhibitor group.
than in the control group: 4.3% versus 1.6% (P=0.001) for nonfatal side-effects, and 5.8% versus 3.8% (P=0.04) for other nonfatal events. The incidence of death or nonfatal episodes of cardiovascular disease did not differ significantly between the groups.

The rates of survival without ESRD and survival without the combined outcome of doubling of serum creatinine or ESRD were greater in the ACE inhibitor group than in the control group. The unadjusted RRs for these outcomes in the ACE inhibitor group were 0.63 (95% CI: 0.47, 0.85) and 0.64 (95% CI: 0.51, 0.80), respectively. The unadjusted RRs for death and the combined outcome of ESRD or death were 1.77 (95% CI: 0.85, 3.70) and 0.76 (95% CI: 0.54, 1.07), respectively.

The baseline patient characteristics that were found to be independently associated with an increased risk of ESRD in the multivariate model were younger age, female gender, higher serum creatinine concentration, higher systolic BP and higher urinary protein excretion. After adjustment for these covariates, the treatment effect remained significant: the RRs for ESRD or the combined outcome of doubling of baseline serum creatinine or ESRD were 0.62 (95% CI: 0.45, 0.85) and 0.59 (95% CI: 0.47, 0.74), respectively, in the ACE inhibitor group.

Patients with a greater urinary protein excretion at baseline benefited more from ACE inhibitor therapy (P=0.03 and P=0.001 for ESRD and the combined outcome, respectively), but the data were inconclusive as to whether the benefit extended to patients with a baseline urinary protein excretion of less than 0.5 g/day.

Authors' conclusions
Antihypertensive regimens that included ACE inhibitors were more effective than regimens without ACE inhibitors in slowing the progression of nondiabetic renal disease. The beneficial effect of ACE inhibitors is mediated by factors in addition to decreasing BP and urinary protein excretion, and is greater in patients with proteinuria. Angiotensin-converting inhibitors are indicated for the treatment of nondiabetic patients with chronic renal disease and proteinuria and, possibly, those without proteinuria.

CRD commentary
The authors addressed a clear review question, which was well-defined in terms of the interventions, participants, study designs and outcome measures to be assessed. The literature search was adequate, although it was restricted to one database and English language studies. However, the authors made considerable effort to contact all the trialists to locate additional published and unpublished trials. The authors noted that the data from three small RCTs that did not provide data on the outcomes were not included. The eligibility of the trials for inclusion was verified through contact with the trial investigators, and it is therefore unlikely that inappropriate studies were included in the review. The validity assessment was appropriate, and the data cleaning was undertaken independently by more than one author and crosschecked against the tables in published and unpublished reports. More than one author extracted the data and, again, the data were checked against that in the reports. The statistical analysis was appropriate and differences between the studies in terms of withdrawals, time when the baseline characteristics were measured and the type of control group, were adequately explored. Overall, the authors' results and conclusions are consistent with the evidence base reviewed.

Implications of the review for practice and research
Practice: The authors stated that ACE inhibitor therapy is indicated for most patients with chronic renal disease.

Research: The authors stated that the results of short-term studies have been used to infer the efficacy of treatment effects for a chronic disease. Longer term follow-up of patients is therefore warranted in order to assess whether ACE inhibitors are beneficial over a longer period of time.

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