Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials

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Authors' objectives
To assess the effect of angiotensin-converting enzyme (ACE) inhibitors on the development of end-stage renal disease caused by factors other than diabetes.

Searching
MEDLINE was searched for relevant English language studies published between 1977 and May 1996. References, review articles and abstracts from recent US and international congresses were searched. Contact was made with investigators who had experience of conducting trials studying the effect of anti-hypertensive agents on the progression of renal disease. Other published or unpublished reports were sought.

Study selection
Study designs of evaluations included in the review
Published and unpublished randomised controlled trials (RCTs) on the effect of ACE inhibitors on renal disease in humans were included if they fulfilled the following criteria: most patients had non-diabetic renal disease, the length of planned follow up was at least one year and the number of patients who developed end-stage renal disease, died or dropped out was reported. Excluded were studies of patients with predominantly diabetic renal disease or who had renal transplants.

Specific interventions included in the review
ACE inhibitors studied included enalapril, captopril, cilazepril and benazepril. Control groups received placebo, beta-adrenergic blockers, calcium channel blockers and unspecified combinations of anti-hypertensive agents. Various anti-hypertensive medications other than ACE inhibitors were added to both these regimes, including beta-adrenergic blockers, calcium channel blockers, diuretics, peripheral alpha-adrenergic blockers, central alpha-adrenergic blockers and vasodilators.

Participants included in the review
Patients had mainly non-diabetic renal disease of varying aetiology including hypertensive nephrosclerosis, glomerular disease, interstitial disease, polycystic kidneys and other causes. Two studies included patients with diabetic nephropathy. Most patients were men (range 48% to 77% in individual studies). The mean age ranged from 44 years to 66 years. The mean baseline impairment of renal function ranged from 1.0 mg/dL to 4.4 mg/dL. Patients were not required to have hypertension or renal insufficiency at baseline.

Outcomes assessed in the review
The following four outcomes were assessed: end-stage renal disease (measured by the initiation of dialysis or transplantation), death, combined outcome of end-stage renal disease or death and drop-out.

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 authors do not state that they assessed validity.

Data extraction
Two authors extracted data on the four outcome measures. The outcome measures were summarised for each randomly-assigned group and the summary sent to the principal investigator with a request for verification, provision of missing data, updated results and individual patient data. For each study the relative risk was calculated for each outcome in the ACE inhibitor group compared with the control group.

**Methods of synthesis**

How were the studies combined?

The pooled relative risk (RR) for each outcome was computed using the random-effects model of DerSimonian and Laird. Mean baseline and follow-up blood pressures of the treatment groups were weighted by the number of patients in each group. The decline in weighted mean blood pressures from baseline to follow-up was calculated in both groups. The difference between groups was calculated as the weighted mean decreases in blood pressure.

How were differences between studies investigated?

Heterogeneity in RR among studies was assessed using the chi-squared test. Meta-regression analysis was used to determine if characteristics of the sample in each study was related to the RR for end-stage renal disease in that study. Characteristics examined included percentage of male patients, mean patient age, percentage of patients with nephrosclerosis, glomerular disease, interstitial disease, polycystic kidneys and other or unknown conditions, mean serum creatinine, mean glomerular filtration rate, mean systolic and diastolic pressures and planned duration of follow-up. Univariate linear regression analysis was used to examine the effect of selected baseline variables and the difference in blood pressure between the treatment groups on the RR expressed on a logarithmic scale.

**Results of the review**

Ten RCTs (1,594 patients) were included.

Weighted mean baseline systolic blood pressures were 150.1 mmHg in the ACE inhibitor group and 151.0 mmHg in the control group. Weighted mean baseline diastolic blood pressures were 91.7 mmHg in ACE inhibitor group and 91.9 mmHg in the control group. Decline in weighted mean systolic blood pressure was 4.9 mm Hg greater in ACE inhibitor group. Decline in weighted mean diastolic blood pressure was 1.2 mm Hg greater in ACE inhibitor group.

End-stage renal disease: pooled RR = 0.70 (95%CI: 0.51, 0.97). Heterogeneity > P > 0.5. For the seven published studies pooled RR = 0.65 (95%CI: 0.45, 0.94). For the seven studies using enalapril RR = 0.74 (95%CI: 0.52, 1.05).

Death: pooled RR = 1.24 (95%CI: 0.55, 2.83). Heterogeneity P > 0.2. For one study with a high relative risk RR = 7.55 (95%CI: 0.95, 60.00), remaining studies RR = 0.89 (95%CI: 0.36, 2.17). Combined end-stage renal disease or death: pooled RR = 0.80 (95%CI: 0.55, 1.17). After omitting one study with a high relative risk RR =0.70 (95%CI: 0.52, 0.94).

Number of drop outs: pooled RR = 1.16 (95%CI: 0.91, 1.47).

Association of baseline factors with the effect of ACE inhibitors on end-stage renal disease: Except for baseline renal function this analysis had limited power because the variability in these factors across studies was not great. Regression coefficient of baseline glomerular filtration rate on the logarithm of the RR was for 10 studies 0.017(95%CI: -0.0063, 0.041);regression coefficient of mean baseline serum creatinine level (10 studies) was -0.096 (95%CI: -0.48, 0.29).

Association of the RR for end-stage renal disease in the ACE inhibitor group in each study, with the observed difference between groups in the decline in systolic and diastolic blood pressures, blood pressure during follow-up: decrease in diastolic blood pressure regression coefficient was -0.007 (95%CI: -0.13, 0.11), decrease in systolic blood pressure regression coefficient was -0.004 (95%CI: -0.21, 0.20).

**Authors’ conclusions**

Angiotensin-converting enzyme inhibitors are more effective than other anti-hypertensive agents in reducing the development of end-stage nondiabetic renal disease and they do not increase mortality. It could not be determined whether this beneficial effect was due to the greater decline in blood pressure or to other effects of ACE inhibition.
CRD commentary
This is a clearly-written and presented review. Though the literature search was limited to English language studies, contact with investigators in the field should have unearthed most relevant studies. Inclusion criteria for primary studies were stated and outcome measures were defined. Methods were used to avoid duplication of data. Details are given of the thorough data extraction and verification methods. Heterogeneity was assessed statistically and potential causes investigated using regression analysis. Sensitivity analysis was done by restricting the analysis to published studies. The discussion included mention of some limitations of the review, including differences in patients baseline characteristics, lack of uniform data on other outcomes such as rates of decline in renal function and lack of individual patient data. The methods used to select studies are not stated and no mention is made of the validity of the included studies.

Had the review included an evaluation of the validity of the primary studies supporting the quality of the primary evidence, the conclusions would have been justified by this otherwise thorough review.

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