Meta-analysis: effect of ACE-inhibitors on outcomes in patients with renal insufficiency

Terajima T, Yamagata S, Satoh N, Ueda S

CRD summary
This review assessed the efficacy of angiotensin-converting enzyme (ACE) inhibitors in slowing the progression to end-stage renal failure in patients with renal disease. The authors concluded that ACE inhibitors are effective in slowing the progression of renal insufficiency regardless of baseline serum creatinine levels. Poor reporting of the review process makes it difficult to verify this conclusion.

Authors' objectives
To determine the effect of angiotensin-converting enzyme (ACE) inhibitors in slowing progression to end stage renal failure (ESRF) in patients with renal disease.

Searching
MEDLINE (from 1966 to 2001) and Igaku-Chuo-Zasshi (from 1987 to 2002) were searched for publications in English or Japanese. The reference lists of retrieved studies, relevant review articles and the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2000) were checked for additional studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with a follow-up of at least one year were eligible for inclusion.

Specific interventions included in the review
Studies of ACE inhibitors were eligible for inclusion. The ACE inhibitors used in the included studies were enalapril, captopril, ramipril, benazepril, lisinopril and cilazapril. The comparators used in the included studies were placebo, beta-blockers (atenolol and acebutolol), conventional treatment (defined as medications with unspecified conventional antihypertensive drugs, excluding angiotensin- receptor blockers) and calcium-channel blockers (nifedipine).

Participants included in the review
Studies of patients aged over 16 years with diabetic or nondiabetic chronic renal disease were eligible for inclusion. The mean age of the participants ranged from 34.5 to 65 years. Patients with renovascular disease (including renovascular hypertension and renal artery stenosis) and chronic congestive heart failure were excluded from the review, as were patients with ESRF who were undergoing dialysis, post-kidney transplantation, or nephrectomy. Patients with a history of allergy to ACE inhibitors and women who were pregnant were also excluded.

Outcomes assessed in the review
Studies evaluating ESRF and serum creatinine (Scr) levels were eligible for inclusion. If the Scr level was unavailable, the glomerular filtration rate was used. The Scr levels were used to determine renal function deterioration. In the review, a two-fold deterioration of renal function was defined as a doubling of the Scr concentration (DScr) of more than 50% from the baseline during follow-up.

How were decisions on the relevance of primary studies made?
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
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Data on the number of participants who progressed to ESRF and the number of participants with a deterioration of renal function were extracted from each individual study and used to calculate an odds ratio (OR). If a study had zero events a value of 0.5 was added to each event cell. The data were extracted on an intention-to-treat basis.

**Methods of synthesis**

**How were the studies combined?**

The results from the individual studies were combined in a fixed-effect meta-analysis using the method of Mantel-Haenszel. A pooled OR and 95% confidence interval (CI) were calculated separately for ESRF and DScr when the studies were sufficiently homogeneous.

**How were differences between studies investigated?**

Heterogeneity was assessed using the Q statistic, with a P-value of less than 0.05 considered significant. Separate analyses were performed for placebo-controlled trials and active comparator trials (including type of comparator). Subgroup analyses were performed according to the baseline level of Scr: below 2 mg/dL, greater than or equal to 2 mg/dL but less than 3 mg/dL, and more than 3 mg/dL.

**Results of the review**

Fifteen RCTs (n=2,484) were included in the review.

**ESRF.**

ACE inhibitors significantly reduced progression to ESRF (OR 0.59, 95% CI: 0.45, 0.77). There was no evidence of statistical heterogeneity (P=0.93). The subgroup analysis according to baseline Scr level found that the reduction in ESRF remained significant in patients with values greater than or equal to 2 mg/dL but less than 3 mg/dL (OR 0.53, 95% CI: 0.45, 0.82) and levels greater than 3 mg/dL (OR 0.53, 95% CI: 0.32, 0.87), but was not significant in those with levels below 2 mg/dL (OR 0.77, 0.46, 1.31). There was no evidence of statistical heterogeneity across subgroups.

ACE inhibitors were associated with a significant reduction in progression to ESRF compared with placebo (OR 0.59, 95% CI: 0.42, 0.83), based on 9 RCTs (1,699 patients). A subgroup analysis according to baseline Scr levels found that the progression to ESRF remained significant when the baseline levels were greater than or equal to 2 mg/dL but less than 3 mg/dL (OR 0.55, 95% CI: 0.35, 0.85), but was not significant in those with levels below 2 mg/dL (OR 0.65 95% CI: 0.37, 1.15) or greater than 3 mg/dL (OR 0.67, 95% CI: 0.22, 2.06). There was no evidence of statistical heterogeneity across subgroups.

ACE inhibitors were not associated with a significant reduction in progression to ESRF compared with conventional treatment (OR 0.57, 95% CI: 0.24, 1.35), beta-blockers (OR 0.70, 95% CI: 0.33, 1.47), or calcium-channel blockers (OR 0.44, 95% CI: 0.17, 1.19); these results were based, respectively, on 2 RCTs (201 patients), 3 RCTs (463 patients) and 1 RCT (121 patients). There was no evidence of statistical heterogeneity. A subgroup analysis according to baseline Scr levels found that progression to ESRF was significant when baseline levels were greater than 3 mg/dL (OR 0.50, 95% CI: 0.29, 0.87). No further analyses were reported.

Renal function deterioration. ACE inhibitors were associated with a significant reduction in renal function deterioration compared with placebo (OR 0.49, 95% CI: 0.35, 0.68), based on 6 RCTs (1,450 patients). There was no evidence of statistical heterogeneity (P=0.84). A subgroup analysis according to baseline Scr level found that the results were only significant in those with levels below 2 mg/dL (OR 0.55, 95% CI: 0.33, 0.93), but there was significant heterogeneity in those with levels greater than or equal to 2 mg/dL but less than 3 mg/dL (P<0.05).

**Adverse events.**

No difference in mortality was found between ACE inhibitors and the comparators. The authors stated that most deaths were due to non-renal factors. Subgroup analyses found no differences according to baseline Scr levels. More patients...
treated with ACE inhibitors experienced a cough or hyperkalaemia compared with those given a comparator.

Authors’ conclusions
ACE inhibitors are effective in slowing the progression of renal insufficiency in patients with baseline Scr levels below or above 3 mg/dL.

CRD commentary
The review addressed a clear research question using what appear to have been appropriate inclusion criteria. Several sources were used to identify both published and unpublished studies, although the search was restricted by language. The authors did not state whether methods were used to minimise bias in the study selection and data extraction processes; the possibility of selection bias and reviewer bias or error cannot, therefore, be ruled out. In addition, since no formal quality assessment was performed, it is not possible to assess the validity of the included studies.

Adequate details of the characteristics of each of the included studies were provided in the report. Based on the evidence presented, the decision to statistically pool the results appears appropriate. The authors formally assessed heterogeneity and performed subgroup analyses to account for clinical differences across the included studies. There is evidence to support the authors’ conclusion. However, it should be noted that the progression to ESRF was not significantly reduced in studies that compared ACE inhibitors with active controls, nor was it significantly reduced for each subgroup analysis according to baseline Scr levels. Furthermore, poor reporting of the conduct of the review means it is difficult to verify the authors’ conclusion.

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

Research: The authors stated that they plan to conduct further research to define the risks and benefits of treatment with ACE inhibitors in patients with different renal dysfunction. They also aim to determine the most effective type of ACE inhibitor and the initial dose required to treat renal insufficiency.

Bibliographic details

Indexing Status
Subject indexing assigned by CRD

MeSH
Angiotensin-Converting Enzyme Inhibitors /therapeutic use; Ventricular Dysfunction, Left /drug therapy

AccessionNumber
12003006982

Date bibliographic record published
28/02/2005

Date abstract record published
28/02/2005

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.