Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors: a meta-analysis of individual patient data

The ACE Inhibitors in Diabetic Nephropathy Trialist Group

Authors' objectives
To determine whether the response of the albumin excretion rate to angiotensin-converting enzyme (ACE) inhibitors has a threshold in patients with type 1 diabetes mellitus and microalbuminuria, and to examine the treatment effect according to covariates.

Searching
MEDLINE was searched and the bibliographies of recent studies and a previous meta-analysis were scrutinised. Key investigators were approached and asked to identify other studies not located through the searches.

Study selection
Study designs of evaluations included in the review
The review included individual patient data (IPD) from randomised controlled trials (RCTs). To be eligible for inclusion, the studies had to involve at least ten patients and have at least one year of follow-up.

Specific interventions included in the review
Studies in which ACE inhibitors were compared with placebo or a non-intervention control group were eligible for inclusion. The following treatment regimes were included: captopril, 12.5 to 50 mg, twice daily; lisinopril, 10 to 20 mg/day; enalapril, 2 mg/day; perindopril, 2 mg/day; and ramipril, 1.25 or 5 mg/day. The treatment duration, where reported, ranged from 0 to 52 years.

Participants included in the review
Non-hypertensive patients with type 1 diabetes mellitus, as defined by the individuals trials, were eligible for inclusion. Patients could only have microalbuminuria, which was defined as an albumin excretion rate of 20 to 200 microg/minute at baseline. The age of the patients ranged from 15 to 68 years.

Outcomes assessed in the review
Studies in which albumin excretion rate was measured at baseline and at one or more follow-up visits were eligible for inclusion. The primary outcome of interest was the change in log albumin excretion rate.

How were decisions on the relevance of primary studies made?
The authors do not state how the relevance of the trials was established.

Assessment of study quality
The authors do not report how the data were checked for inclusion in the analysis. The authors do not state how decisions were made on whether to include or exclude trials.

Data extraction
The following data were requested from the trial investigators for each patient included in the trial: age, duration of diabetes, gender, treatment assignment at baseline, and baseline and follow-up data on albumin excretion rate, blood-pressure and glycaemic control. Additional tabulated data included the mean age and the mean treatment duration, and their respective ranges.

Methods of synthesis
How were the studies combined?
The meta-analysis was performed in two ways. First, a trial-level analysis was performed in which the treatment differences in the summary measure, adjusted for the baseline albumin excretion rate, were calculated for each trial. The estimate and the associated standard errors were used to obtain an overall estimate of the treatment effect. Both fixed-effect and random-effects methods were used (see Other Publications of Related Interest nos.1-2), and estimates of the between-trial variance were obtained (see Other Publications of Related Interest no.3). A patient-level analysis was also performed, using random-effects regression models in which the summary outcome measure for each patient was adjusted for the baseline albumin excretion rate (see Other Publications of Related Interest no.4). Dummy variables representing each trial were also included in all models. The estimate for the treatment effect was expressed as a percentage difference.

The absolute rates of progression to macroalbuminuria and regression to normoalbuminuria were considered as outcomes. The odds ratios (ORs) were estimated from fixed-effect and random-effects models.

How were differences between studies investigated?
The between-trial variance was estimated from both fixed-effect and random-effects models (see Other Publications of Related Interest no.3).

Results of the review
IPD from 12 RCTs were included (n=698).

Estimated effect at 2 years for studies with at least 2 years of follow-up (10 studies, n=646): all the studies demonstrated a marked beneficial effect of ACE inhibitors on the rate of change in albumin excretion rate. Using data from the patient-level regression model, the albumin excretion rate was 51.2% (95% confidence interval, CI: 33.6, 64.2) lower in those receiving ACE inhibitors when using the fixed-effect model and 50.2% (95% CI: 30.0, 64.6) lower when using the random-effects model.

Adjustment for baseline covariates: the separate addition of covariates such as age, gender, duration of diabetes, in addition to the initial adjustment of baseline albumin excretion, had no impact on the treatment effect.

Change in systemic blood-pressure and albumin excretion rate: when adjustment was made for changes in blood-pressure and albumin excretion rate, the treatment effect was attenuated from 50.7% (95% CI: 29.8, 65.4) to 45.1% (95% CI: 18.6, 63.1).

Effect of baseline albumin excretion rate: the estimated 2-year difference in albumin excretion rate was 74.1% in patients whose baseline albumin excretion rates were at the upper boundary of microalbuminuria (200 microg/minute), compared with just 17.8% in those who were at the lower boundary of microalbuminuria (20 microg/minute) at baseline (p=0.04).

Progression to macroalbuminuria and regression to normoalbuminuria: with the exception of one study, each trial demonstrated a beneficial effect and the fixed-effect model showed an overall OR of 0.38 (95% CI: 0.25, 0.57, p<0.001) in favour of ACE inhibitors. Regression to normoalbuminuria was greater in treated patients (fixed-effect OR 3.07, 95% CI: 2.15, 4.44, p<0.001)

Authors’ conclusions
In normotensive patients with type 1 diabetes mellitus and microalbuminuria, ACE inhibitors significantly reduced progression to macroalbuminuria and increased the chances of regression. Beneficial effects were weaker at the lowest levels of microalbuminuria, but did not differ according to other baseline risk factors. Changes in blood-pressure cannot entirely explain the antiproteinuric effect of ACE inhibitors.

CRD commentary
The authors reported clear inclusion and exclusion criteria in terms of the interventions, participants, outcomes and study design. The search strategy was limited to one database, but key investigators were approached in order to
identify further trials. The authors did not report how the decision to include studies was taken and whether the data were checked or analysed. The meta-analysis of patient data was carried out appropriately, but there was no clear assessment or exploration of heterogeneity.

Given the limitations outlined, the authors’ conclusions are supported by the results presented.

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

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**Other publications of related interest**

This additional published commentary may also be of interest. Mahon JL. Review: angiotensin converting enzyme inhibitors are beneficial in type 1 diabetes mellitus and microalbuminuria regardless of baseline risk factor status. Evid Based Med 2001;6:146.

**Indexing Status**
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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.