The impact of renin-angiotensin-aldosterone system inhibitors on Type 1 and Type 2 diabetic patients with and without early diabetic nephropathy

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CRD summary
The authors concluded that renin angiotensin aldosterone system inhibitors (RAASI) reduced urinary albumin excretion for type 1 diabetic patients with microalbuminuria but not with normoalbuminuria and for type 2 diabetic patients with and without microalbuminuria. This appeared to be a well conducted review but it is difficult to assess the reliability of the findings without further information about the quality of the studies.

Authors' objectives
To assess the impact of renin angiotensin aldosterone system inhibitors (RAASI) on urinary albumin excretion in patients with type 1 or type 2 diabetes with or without microalbuminuria.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from January 2005 to August 2010; search terms were provided in an online appendix. Reference list of relevant reviews (for trials published before 2005) and trials were searched. Unpublished trials were sought from authors of trials published since 2000.

Study selection
Eligible studies were randomised controlled trials (RCTs) of at least six months duration that compared angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) (collectively known as RAASI) with placebo, no treatment or another antihypertensive other than an ACE inhibitor or ARB. Eligible studies were conducted in patients with type 1 and type 2 diabetes and reported results for each type separately. Outcomes of interest were urinary albumin excretion at the end of the trial, progression to microalbuminuria, progression to macroadalbuminuria, regression to normoalbuminuria (all defined in the paper), change in glomerular filtration rate and death. Eligible trials had to report at least one of the outcomes separately for patients with normoalbuminuria or micro/macroalbuminuria. Urinary albumin levels had to be reported either as a timed albumin excretion rate or as a spot test albumin-creatinine ratio.

Details on study participants were not reported. Drugs and their dosages were presented in a table.

Two reviewers independently selected studies for inclusion. Any disagreements were resolved by consensus with a third reviewer.

Assessment of study quality
The authors did not explicitly state that they assessed validity but they evaluated aspects of quality criteria in their sensitivity analyses and noted methods of randomisation in their discussion, which suggested that some assessment was made.

Data extraction
Outcomes were extracted from each study to calculate relative risk (RR) or mean difference and 95% confidence intervals (CIs). Data were imputed for some studies. Trials that evaluated both an ACE inhibitor and an ARB in comparison with placebo or another treatment were included in the meta-analysis by splitting data from the comparator group.

Two reviewers independently extracted data. Any disagreements were resolved by consensus with a third reviewer.

Methods of synthesis
Trials were pooled using fixed-effect and random-effects models. Heterogeneity was assessed using the I² statistic. Sensitivity analysis was conducted on whether or not a trial clearly stated that it was double-blinded and whether or not...
it was clearly stated that at least two measurements were made to categorise patients as normoalbuminuric, microalbuminuric and macroalbuminuric and by sample size (fewer than 200 patients). A random-effects meta-regression was undertaken to evaluate the explanatory value of baseline urinary albumin and medication type on the effect size for type 1 and type 2 diabetes patients separately. Multivariate meta-regression (post hoc) and subgroup analyses were conducted to explore heterogeneity.

Results of the review
Forty-nine trials (34,082 participants) were included in the review. Twenty-one trials were in patients with type 1 diabetes (5,413 were included in the review) and 29 in patients with type 2 diabetes (28,669 participants). Methods of randomisation were not reported for most of the trials.

Type 1 diabetes: In patients who were normoalbuminuric at baseline, the ratio of mean urinary excretion was not significantly different between treatment and control (0.94, 95% CI 0.79 to 1.12; I² not reported; seven studies; random-effects model). In patients who were microalbuminuric at baseline there was a significant effect in favour of treatment (0.33, 95% CI 0.23 to 0.46; 14 studies).

Type 2 diabetes: In patients who were normoalbuminuric at baseline the ratio of mean urinary excretion was significantly different between treatment and control in favour of treatment (0.79, 95% CI 0.68 to 0.93; seven studies). In patients who were microalbuminuric at baseline there was a significant effect in favour of treatment (0.73, 95% CI 0.62 to 0.85; 21 studies).

Results of subgroup analyses were presented in the paper and in an online appendix. For patients with type 1 diabetes, RAASI treatment of normoalbuminuric patients led to no significant difference in the number of patients who progressed to microalbuminuria from the comparator group. For patients with type 2 diabetes, RAASI treatment of normoalbuminuric patients led to significantly fewer patients who progressed to microalbuminuria (RR 0.84, 95% CI 0.79 to 0.89; I²=19%; eight studies).

In trials that included patients with type I and with type 2 diabetes, RAASI treatment of patients with microalbuminuria resulted in significantly fewer progressing to macroalbuminuria (RR 0.39, 95% CI 0.23 to 0.64; I²=0%; seven studies for type 1 and RR 0.52, 95% CI 0.43 to 0.63; I²=48%; eight studies for type 2) and in more patients regressing from microalbuminuria to normoalbuminuria (RR 5.81, 95% CI 2.05 to 16.43; I²=0%; four studies for type 1 and RR 1.20, 95% CI 1.12 to 1.29; I²=75%; eight studies for type 2).

There was no significant effect of treatment on mortality or glomerular filtration rate in any of the trials in patients with type 1 or type 2 diabetes.

Results of meta-regression were presented; no single factor could explain the heterogeneity between the trials.

Authors’ conclusions
RAASI reduced urinary albumin excretion for type 1 diabetic patients with microalbuminuria but not those with normoalbuminuria. Treatment reduced urinary albumin excretion for type 2 diabetic patients with and without microalbuminuria.

CRD commentary
The review question and inclusion criteria were clear. There was a comprehensive search for published and unpublished literature. Steps were taken in the review process to minimise reviewer error and bias. It appeared that a quality assessment may have been done but the results were not reported. The authors noted that the poor methodological reporting was a limitation of their review. Data were appropriately pooled and heterogeneity was assessed.

This appeared to be a well conducted review but it is difficult to assess the reliability of the findings without further information about the quality of the studies.

Implications of the review for practice and research
Practice: The authors stated that this review did not provide evidence for routine use of RAASI for type 1 normoalbuminuric diabetes patients.
Research: The authors stated that the current review raised the possibility that monitoring for type 2 diabetes could be replaced by routine treatment with RAASI for type 2 diabetes. Before this was considered, further research on monitoring (including cost-effectiveness and a full health economic analysis) was needed.

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