Effects of renin-angiotensin system blockers on renal outcomes and all-cause mortality in patients with diabetic nephropathy: an updated meta-analysis

Sarafidis P A, Stafylas P C, Kanaki A I, Lasaridis A N

CRD summary

This review investigated angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in diabetic nephropathy. The authors concluded that treatment reduced the risk of end-stage renal disease and doubling of serum creatinine, but did not affect all-cause mortality. The reliability of the authors' conclusions is unclear as the quality of the included studies was not reported.

Authors' objectives

To investigate the effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with diabetic nephropathy.

Searching

MEDLINE via PubMed and EMBASE were searched from 1977 to June 2007 for English-language articles published in peer-reviewed journals. Search terms were reported. Reference lists of retrieved articles including meta-analyses and reviews were also examined for additional studies.

Study selection

Randomised controlled trials (RCTs) of at least one-year duration that compared an angiotensin-converting enzyme inhibitor-based regimen with regimens that did not include these medications (placebo, placebo plus antihypertensive treatment or antihypertensive treatment that did not include a renin-angiotensin-aldosterone blocker) in adults with diabetic nephropathy were eligible for inclusion. Individuals with any type of diabetes and any stage of diabetic nephropathy were eligible. To be included in the review, studies also had to assess incidence of end-stage renal disease and/or death from any cause. The outcome doubling of serum creatinine was also of interest. The included studies were of patients with type 1 and/or type 2 diabetes with micro and/or macro albuminuria. Most studies had patients with hypertension at baseline (where reported). The angiotensin-converting enzyme inhibitor-based treatments varied by drug (for example, captopril, enalapril, lisinopril). Dose ranged from 1.25mg to 100mg per day. The angiotensin receptor blocker-based treatments investigated valsartan, irbesartan and losartan. Doses ranged from 50mg to 300mg per day. Follow-up duration was 12 to 60 months in the included studies.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality

Methodological quality of the included studies was assessed in terms of allocation concealment, intention to treat analysis, loss to follow up and blinding. Two reviewers independently assessed study quality and disagreements were resolved by consensus.

Data extraction

The outcomes were summarised as relative risks and risk differences with 95% confidence intervals (CIs). Data were extracted independently by two reviewers and disagreements resolved by consensus.

Methods of synthesis

Relative risks and risk differences were pooled using a DerSimonian and Laird random-effects model if statistically significant heterogeneity was present or Mantel-Haenszel fixed-effects model. Statistical heterogeneity was assessed using the Cochrane Q test and I^2 statistic. The number needed to treat to prevent one case of end-stage renal disease was calculated using risk differences. Publication bias was assessed using a funnel plot , Begg's rank correlation test and Egger's test.

Results of the review

Twenty-four RCTs were included in the review (n=10,610): 20 of angiotensin-converting enzyme inhibitor-based treatment (n=7,269); and four of angiotensin receptor blocker-based treatment (n=3,341).

There was no evidence of publication bias.

Angiotensin-converting enzyme inhibitor treatment was associated with a significant decrease in doubling of serum creatinine compared with control (relative risk 0.71, 95% CI: 0.56 to 0.91, p=0.006; eight RCTs, n=6,754), but no significant decrease in end-stage renal disease.

Angiotensin receptor blocker treatment was associated with a significant decrease in end-stage renal disease (relative risk 0.78, 95% CI: 0.67 to 0.91, p=0.002; three RCTs, n=3,251) and doubling of serum creatinine (relative risk 0.79, 95% CI: 0.68 to 0.91, p=0.001; three RCTs, n=3,251).

No significant difference in mortality was found between angiotensin-converting enzyme inhibitor or angiotensin receptor blocker groups and control. No significant heterogeneity was found.

The number needed to treat for prevention of one case of end-stage renal disease for patients that received angiotensin-converting enzyme inhibitors was 333 (not significant, p=0.61) and for angiotensin receptor blockers was 21 (p=0.002).

Significant heterogeneity was found for risk differences of studies of angiotensin-converting enzyme inhibitors for end-stage renal disease.

Authors' conclusions

Renin-angiotensin-aldosterone blocker treatment of patients with diabetic nephropathy reduced the risk of end-stage renal disease and doubling of serum creatinine, but did not affect all-cause mortality.

CRD commentary

The research question was supported by clear inclusion criteria for participants, intervention, study design and outcomes. Two relevant databases were searched. Searches were restricted to English-language studies and the authors did not report any attempts to find unpublished studies, which increased the possibility of publication and language biases (although no evidence of publication bias was found). Validity assessment and data extraction were performed in duplicate, which minimised the risk or error and bias; it was not reported whether similar steps were taken for data extraction. Statistical heterogeneity was assessed and taken into consideration by the authors. Pooling of studies appeared appropriate except for the number needed to treat analysis (where statistical heterogeneity was present). Although study quality was assessed, the results were not reported and so the reliability of the study results, and hence any synthesis from them, could not be determined

Implications of the review for practice and research

Practice: The authors stated that the findings supported the current recommendations that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be used as first-line antihypertensives and should be used interchangeably in patients with diabetic nephropathy.

Research: The authors stated that well-designed trials that compared angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with overt diabetic nephropathy were needed.

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