Effects of renin-angiotensin system blockades on cardiovascular outcomes in patients with diabetes mellitus: a systematic review and meta-analysis


CRD summary
Renin-angiotensin system blockades reduced risk of myocardial infarction and major cardiovascular events in patients with diabetes mellitus. A substantial proportion of included data were based on post hoc analyses so the authors conclusions may not be reliable.

Authors' objectives
To examine the efficacy of renin-angiotensin system blockades for cardiovascular outcomes in patients with diabetes mellitus.

Searching
MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to June 2010 for English language publications; search terms were reported. References of included articles and reviews were checked. ClinicalTrials.org and the US Food and Drug Administration website were searched for unpublished trials.

Study selection
Randomised controlled trials (including post-hoc analyses) of adults (18 years or over) with diabetes mellitus who received renin-angiotensin system blockade – angiotensin converting enzyme (ACE) inhibitors or angiotension receptor blockers (ARBs) – compared to placebo or other drugs were eligible for inclusion. Studies were required to assess cardiovascular outcomes with median or mean follow-up of more than a year. Studies on patients with acute coronary syndrome or chronic renal failure on dialysis were excluded. Studies that compared ACE-inhibitors with ARBs, compared efficacy of different dosages of renin-angiotensin system blockade or examined combined treatment that included renin-angiotensin system blockade were excluded. Studies of poor quality were excluded.

Mean age ranged from 55 to 76 years. Baseline blood pressure was above 140/90mmHg in almost all studies. Baseline haemoglobin A1c was reported in only half of the included studies and ranged from 7% to 11.6%.

Two reviewers independently selected studies for inclusion. Disagreements were resolved through discussion.

Assessment of study quality
Studies were rated as good, fair or poor based on AHRQ (Agency for Healthcare Research and Quality) criteria for randomisation methods, outcomes used, statistical analysis methods, selective reporting/errors in reporting and attrition.

The authors did not state how many reviewers conducted the quality assessment.

Data extraction
Outcomes included fatal and non-fatal myocardial infarction and stroke. Major cardiovascular events were defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. Adverse events were examined. Data were extracted from each study to calculate risk ratios and 95% confidence intervals (CIs).

Two reviewers independently extracted data. Disagreements were resolved through discussion.

Methods of synthesis
Studies were pooled using a random-effects model. Heterogeneity was assessed using $I^2$ (25% low, 50% moderate and 75% high).

A meta-regression was conducted to assess the impact of blood pressure changes on myocardial infarction. Heterogeneity was explored in subgroup analyses for number of patients, length of follow-up, publication date, age, baseline low-density lipoprotein cholesterol, proportion of patients on antihypertensive drugs, patients with obesity and...
patients with coronary heart disease. Publication bias was assessed using a funnel plot and Egger's test.

**Results of the review**

Nineteen trials (17 published and two unpublished) were included in the meta-analyses (44,639 patients). Mean follow-up ranged from 2.5 to 6.1 years (where reported). Data from 11 of the included studies were from subgroup analyses (four planned and seven post hoc). All published trials were rated as fair quality; no information on study quality was provided for unpublished trials. Drop-out was not reported in six trials, was greater than 20% in nine trials and less than 20% in two. Funnel plot and Egger's test showed no evidence of publication bias.

Renin-angiotensin system blockade was associated with a statistically significant reduction in risk of myocardial infarction compared with controls (RR 0.82, 0.72 to 0.94; I²=49%; 19 data points from 17 trials) and reduced risk of a major cardiovascular event approaching statistical significance (RR 0.92, 95% CI 0.86 to 1.00; I²=53%; 21 data points from 19 trials). No statistically significant reductions were found for stroke, cardiovascular death and all-cause mortality.

There was no evidence for an association between blood pressure and cardiovascular outcomes (15 trials).

Subgroup analyses that found studies published before 2003 (but not after 2003) had a statistically significant reduced risk of myocardial infarction for renin-angiotensin system blockade (RR 0.72, 95% CI 0.57 to 0.89). ACE-inhibitors were associated with a statistically significant reduction in risk for myocardial infarction (RR 0.77, 95% CI 0.64 to 0.92) but this was not found for ARBs. No other variables examined in subgroup analyses appeared to impact on heterogeneity.

**Authors' conclusions**

Renin-angiotensin system blockade reduced the risk of myocardial infarction and major cardiovascular events in patients with diabetes mellitus and should be routinely considered for use in this population.

**CRD commentary**

The review question and inclusion criteria were clear. The electronic search included an adequate coverage of relevant sources but only studies published in English were included. There was potential for studies to be missed but this was unlikely to impact on the validity of the results due to the large number of participants included in the meta-analysis. Unpublished material was searched for and included in the analyse, which reduced the risk of publication bias. Appropriate methods to minimise error and bias were used for study selection and data extraction but it was unclear whether this applied for quality assessment.

A substantial proportion of the included studies were based on post hoc analyses and were potentially vulnerable to confounding. This was acknowledged but no sensitivity analyses were conducted to assess the impact of including these studies. There was moderate heterogeneity and potential causes were investigated in subgroup analyses. There appeared to be some minor double counting in the meta-analysis but it seems unlikely that this would strongly impact conclusions.

The inclusion of a large number of post hoc analyses suggested that the authors' conclusions may not be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that renin-angiotensin system blockade should routinely be considered for reducing risk of myocardial infarction and major cardiovascular events in patients with diabetes mellitus.

**Research:** The authors stated that a randomised trial of renin-angiotensin system blockade in diabetic patients with blood pressure below 130/80mmHg would reduce uncertainty on the effectiveness of this intervention beyond blood pressure reduction.

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