Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147,020 patients from randomised trials

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CRD summary
This review concluded that there was no evidence that angiotensin receptor blockers increased the risk of heart attack. Compared with controls (active treatment or placebo) angiotensin receptor blockers reduced the risk of stroke, heart failure and new onset diabetes. The conclusions of this review appear to be reliable, but the variation between the studies in this review needs further exploration.

Authors’ objectives
To evaluate the risk of cardiovascular and other outcomes associated with angiotensin receptor blockers.

Searching
The authors searched PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) up to August 2010 and provided details of the search strategy used. They checked the references of review articles, meta-analyses and identified studies to locate any further studies. No language restrictions were applied. The authors consulted FDA documents related to approval/labelling change and minutes of meetings.

Study selection
Included studies had to be randomised controlled trials (RCTs) that compared angiotensin receptor blockers with placebo or active treatment. Trials needed to enrol at least 100 participants. There was a minimum follow-up of one year. Any of these outcomes could be reported: myocardial infarction, death, cardiovascular death, angina pectoris, stroke, heart failure and new onset diabetes mellitus. Trials in which angiotensin receptor blockers were not used as first-line agents or trials/treatment arms where angiotensin receptor blockers were combined with angiotensin-converting enzyme inhibitors were excluded.

Various angiotensin receptor blockers were used across the included studies. Comparators included placebo, angiotensin-converting enzyme inhibitors, calcium channel blockers and beta blockers. Varying cohorts of patients were enrolled across the trials including (but not restricted to) those with: hypertension, heart failure, diabetes and vascular disease. The proportion of participants with diabetes ranged from 20% to 80%, where recorded. The proportion of participants with hypertension ranged from zero to 100% and most trials enrolled more than 75%. Mean age ranged from 29 years to 76 years. Follow-up ranged from one to 6.5 years (average of 3.3 years).

Two authors independently assessed trial eligibility. Disagreements were resolved by consensus.

Assessment of study quality
Risk of bias was assessed using components recommended by the Cochrane Collaboration: sequence generation of allocation; allocation concealment; blinding of participants, staff and outcome assessors; incomplete outcome data; selective outcome reporting and other sources of bias. Trials with high or unclear risk of bias in any one of the first three components were considered as being at high risk of bias. Otherwise they were assessed as being at low risk of bias.

Two authors independently assessed trial validity. Disagreements were resolved by consensus.

Data extraction
Data were extracted from original publications and FDA dockets. Study authors were contacted where data were unclear or not reported.

Two authors independently extracted data from included studies. Disagreements were resolved by consensus.

Methods of synthesis
Studies were stratified according to comparator (placebo or active treatment). Meta-analyses were performed using intention-to-treat (ITT) data with trials weighted by the inverse variance method. DerSimonian and Laird random-effects models were used. Relative risks (RR) and 95% confidence intervals (CI) were calculated. Heterogeneity was assessed through the I² statistic. Publication bias was estimated with funnel plots and using Begg's and Egger's tests.

Subgroup analyses were conducted based on risk of bias and cohort enrolled (hypertension versus non-hypertension trials). Trial sequential analysis methods were used to assess the robustness of the findings in differing scenarios.

Results of the review
Thirty-seven trials with 39 comparator arms (147,020 participants) were included in the review. Twelve trials were considered at high risk of bias and the others to be at low risk of bias.

Angiotensin receptor blockers were not associated with any increase in the risk of myocardial infarction when compared with controls (RR 0.99, 95% CI 0.92 to 1.07). Results were similar when angiotensin receptor blockers were compared with either placebo or active treatment (p=0.15 for interaction). There was low to moderate heterogeneity and no evidence of publication bias.

Angiotensin receptor blockers were not associated with an increase in risk of death, cardiovascular death and angina when compared with controls. Similar results were observed in comparisons with placebo or active treatment for all of these outcomes (p>0.05 for interaction for all comparisons). There was no to low heterogeneity and no evidence of publication bias for the outcomes of death and cardiovascular death. For angina there was high heterogeneity, but no evidence of publication bias.

Angiotensin receptor blockers were associated with a reduction in risk of stroke (RR 0.90, 95% CI 0.84 to 0.98), heart failure (RR 0.87, 95% CI 0.81 to 0.93) and diabetes (RR 0.85, 95% CI 0.78 to 0.93). Results were similar in comparisons with placebo or active treatment. There was no to moderate heterogeneity and no evidence of publication bias for heart failure and stroke. For new onset diabetes, there was moderate to high heterogeneity and no evidence for publication bias.

Subgroup analysis based on trial quality (low risk of bias versus high risk of bias) and cohort enrolled (hypertension versus non-hypertension trials) identified that the risk reduction of stroke, angina and heart failure was higher in trials at high risk of bias compared with low risk of bias (although directionally similar). The risk reduction for heart failure and new onset diabetes was higher in hypertension trials than in non-hypertension trials (although directionally similar). Other outcomes did not differ.

Based on trial sequential analysis, there was no evidence for an average 5% to 7.5% relative increase in myocardial infarction, death and cardiovascular death. However, there was evidence for a reduction in risk of stroke with angiotensin receptor blockers compared with placebo only and a reduction in risk of heart failure and new onset diabetes with angiotensin receptor blockers compared to controls.

Authors’ conclusions
There was no evidence to support the theory that angiotensin receptor blockers increased the risk of myocardial infarction. Compared with controls (active treatment or placebo) angiotensin receptor blockers reduced the risk of stroke, heart failure and new onset diabetes.

CRD commentary
This review was based on defined inclusion criteria for participants, interventions, outcomes and study design. A number of search methods were used and attempts were made to identify unpublished articles and those in languages other than English. Study validity was assessed and the influence of quality on results investigated. Procedures to minimise bias and error in study selection, data extraction and quality assessment of studies were put in place. Pooling appeared to be appropriate and the authors investigated a number of sources of heterogeneity.

The conclusions of this review appear to be reliable given the evidence presented, but moderate and high levels of heterogeneity in several of the analyses imply that not all potential confounders were explored.

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

Research: The authors stated that an individual patient data meta-analysis (IPD) might better assess any clinically relevant differences in effect size according to different variables.

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