Angiotensin receptor blockers and risk of myocardial infarction: systematic review

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CRD summary
This review found that angiotensin-receptor blockers, when compared with angiotensin-converting enzyme inhibitors or placebo, did not increase the chance of heart attacks in patients at risk of such events. The review's conclusions are in line with the evidence presented, but further prospective trials should clarify the exact risks and benefits of these drugs in various patient groups.

Authors' objectives
To evaluate the effect of angiotensin-receptor blockers (ARBs) on the risk of myocardial infarction (MI) in patients at risk of cardiovascular events.

Searching
MEDLINE, EMBASE and the Cochrane CENTRAL Register were searched from inception to December 2004; the search terms were reported. The reference lists of meta-analyses and review articles were also checked. The trials needed to be published in English.

Study selection

Study designs of evaluations included in the review
Controlled trials were eligible for inclusion in the review.

Specific interventions included in the review
The included trials needed to compare ARBs used as monotherapy with angiotensin-converting enzyme (ACE) inhibitors or placebo. The ARBs included in the review were candesartan, losartan, irbesartan, telmisartan and valsartan.

Participants included in the review
Eligible participants were those at risk of cardiovascular events. The patient groups included those with hypertension, diabetes and nephropathy, heart failure, recent MI or ischaemic syndrome.

Outcomes assessed in the review
To be eligible, trials needed to report MI as either a pre-specified outcome or as an adverse event.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened abstracts for eligibility and separate reviewers independently assessed the full text of the remaining articles. Any disagreements on the inclusion or exclusion of articles were resolved by the vote of a third reviewer.

Assessment of study quality
The aspects of study validity considered were allocation concealment, blinding, intention-to-treat analysis and loss to follow-up. Trials were also scored on the Jadad scale, which measures randomisation, blinding and study withdrawals. It appeared that two reviewers independently assessed study quality, with any disagreements resolved by a third reviewer.

Data extraction
Two reviewers extracted the data onto standardised data collection forms. The accuracy of the data was compared between reviewers. The numbers of patients with reported Mls, fatal or nonfatal, were documented according to the definition used by the authors of the individual studies. The study authors were contacted where numbers of patients with Mls needed to be extracted from composite end points, and where only fatal or nonfatal Mls had been reported.
The best obtainable data were used. For each trial, odds ratios (ORs) and associated confidence intervals (CIs) were calculated.

**Methods of synthesis**

**How were the studies combined?**

The trials were combined using both random-effects and fixed-effect meta-analyses to generate pooled ORs. Primary analyses used the random-effects model. Funnel plots were used to investigate publication bias.

**How were differences between studies investigated?**

Separate pooled ORs were generated for ARBs versus ACE inhibitors and for ARBs versus placebo.

The Q statistic was used to investigate heterogeneity of treatment effects between trials.

**Results of the review**

Nineteen controlled trials with 31,569 patients were included in the review.

Agreement on study inclusion, as measured by the kappa statistic, was 0.75. There was no evidence of publication bias.

Nine trials received the maximum quality score of 5. Allocation concealment was adequate in 8 trials. With the exception of one trial, treatment was randomised. Blinding of the participants was achieved in all 19 trials, investigators in 17 trials and outcome assessors in 18. Intention-to-treat analysis was used in 15 trials.

ARBs did not lead to a statistically significant increase in the risk of MI when compared with placebo (OR 0.94, 95% CI: 0.75, 1.16), based on 11 trials (n=21,062). However statistically significant heterogeneity was noted. When compared with ACE inhibitors, the OR was 1.01 (95% CI: 0.87, 1.16), based on 9 trials (n=10,625). The OPTIMAAL trial of losartan versus captopril in patients with recent MI or ischaemic syndrome accounted for 86.8% of the weighted OR. Analyses using the fixed-effect model gave similar results.

**Authors' conclusions**

Treatment with ARBs was not associated with an increased risk of MI.

**CRD commentary**

The inclusion criteria were defined for patients, interventions, outcomes and study designs. A range of methods was used to locate trials, although unpublished and foreign language articles were not eligible for inclusion. However, tests for publication bias were performed. The trials were assessed for quality but no subgroup analysis based on quality was undertaken. Two reviewers were involved in the review process, thus helping to minimise the introduction of bias into the study selection and data extraction procedures. The pooling of results for ARBs versus placebo was undertaken in the face of significant heterogeneity. It is worth noting that one large trial in patients with recent MI or ischaemic syndrome dominated the comparison of ARBs and ACE inhibitors. The conclusions are in line with the evidence presented, and the authors acknowledged the possibility of larger, prospective trials confirming or refuting the possibility of an increase in MIs with ARBs.

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

Practice: The authors stated that the review supported the safety of ARBs in patients at risk for MI.

Research: The authors stated that larger ongoing trials should clarify the potential for increasing or decreasing the risk of MI using ARBs.

**Bibliographic details**

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