Cardiovascular outcomes in high-risk patients without heart failure treated with ARBs: a systematic review and meta-analysis

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CRD summary
This review found no evidence that angiotensin II type I receptor antagonists (ARBs) conferred cardiovascular protection akin to angiotensin-converting enzyme inhibitors. ARBs may have had a small benefit related to stroke risk, but this was difficult to quantify. The authors’ conclusions reflected the evidence presented, but due to some methodological biases the reliability of the results are unclear.

Authors’ objectives
To determine the impact of angiotensin II type I receptor antagonists (ARBs) on cardiovascular outcomes in high-risk patients without heart failure.

Searching
MEDLINE via PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched from January 1990 to April 2008. Search terms were reported. Reference lists of retrieved articles were scanned for additional studies.

Study selection
Randomised controlled trials (RCTs) of ARBs in comparison with another drugs or placebo that reported data on adverse cardiovascular events including myocardial infarction, stroke, cardiovascular mortality and all-cause mortality were eligible for inclusion.

ARBs used in the included studies included losartan, candesartan, valsartan, irbesartan and telmisartan. Control groups included captopril, atenolol, conventional therapy without angiotensin-converting enzyme inhibitor (ACEI), hydrochlorothiazide, enalapril, amlodipine, lisinopril, enalapril, placebo and conventional therapy and placebo only. Doses varied widely between studies. Follow-up ranged from two weeks to five years. Included studies were of participants with and without heart failure. Participants were treated for heart failure, hypertension, renal dysfunction or diabetes mellitus. Participant ages ranged from three to 80 years.

The authors state neither how papers were selected for inclusion nor how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Data were extracted on myocardial infarction, stroke, cardiovascular mortality and all-cause mortality. Where possible, data were extracted from original publications. When the original publication was not available, data from previous meta-analyses that included the study were used. Data provided by original study authors to previous meta-analysis authors were utilised. Data for each outcome were used to calculate odds ratios (ORs) and 95% confidence intervals (CI).

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
Studies were grouped into heart-failure versus non-heart failure subgroups. Odds ratios were pooled in a meta-analysis using a fixed-effect model where data were homogeneous. Studies were not pooled where there was evidence of statistical heterogeneity. Heterogeneity was assessed using Cochran’s Q statistic. Studies that had no events were excluded from the meta-analysis. An exclusion sensitivity plot and evidence dissemination bias parameters were used to
assess publication bias.

**Results of the review**

Thirty seven RCTs (n=89,901) were included in the review.

There was an increase in myocardial infarction for non heart-failure patients treated with ARB compared to control group, but this only just reached statistical significance (OR 1.09, 95% CI 1.00 to 1.18, p=0.05; 13 RCTs). Rates of myocardial infarction were similar between ARB and control groups in studies with patients with heart failure, but these studies were not pooled due to statistical heterogeneity (OR range 0.05 to 1.61; eight RCTs).

There were no significant differences between ARB and control in patients with or without heart failure for stroke, cardiovascular mortality or all-cause mortality.

There was evidence of significant publication bias in the analyses of non-heart-failure patients, but not for other outcomes.

**Authors’ conclusions**

There was no evidence to suggest that angiotensin II type 1 receptor antagonists (ARBs) conferred cardiovascular protection akin to angiotensin-converting enzyme inhibitors (ACEIs). ARBs may have a small benefit that related to stroke risk, but heterogeneous studies made this difficult to quantify.

**CRD commentary**

The review question was clear and inclusion criteria were defined for study design, interventions, outcomes and patients. Several relevant sources were searched. No specific attempts were made to locate unpublished studies. Formal assessment found evidence of significant publication bias for some outcomes. It was unclear whether language restrictions were applied and so there was potential for language bias. Methods used to select studies and extract data were not reported, so any efforts made to reduce reviewer error and bias were unknown. Study validity was not assessed and so results from these studies and any synthesis may not have been reliable. Studies were combined in a meta-analysis and heterogeneity was assessed. However, the authors did not report the results of tests of heterogeneity and did not explore reasons for heterogeneity. Some data for individual studies were taken directly from other meta-analyses rather than primary studies and the results of these may have been open to error and bias. An addendum reported results of later studies that altered some of the results, but as these were not been included in the main part of the review the data from these has not been reported here. The authors conclusions reflected the evidence presented, but due to some methodological biases their reliability is unclear.

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

**Practice:** The authors stated that as ACEIs protect against both stroke and myocardial infarction, caution is advised in the use of ARBs as a substitute for ACEIs in patients without an indication of heart-failure, but who are tolerant of an ACEI.

**Research:** The authors did not state any implications for research.

**Funding**

None stated.

**Bibliographic details**


**PubMedID**

19178130

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Angiotensin II Type 1 Receptor Blockers /therapeutic use; Angiotensin-Converting Enzyme Inhibitors /therapeutic use; Cardiovascular Diseases /etiology /mortality /prevention & control; Humans; Risk Assessment; Treatment Outcome

**AccessionNumber**
12009103324

**Date bibliographic record published**
22/07/2009

**Date abstract record published**
31/03/2010

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.