Meta-analysis: angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction

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CRD summary
This review evaluated the efficacy of angiotensin-receptor blockers (ARBs) in patients with chronic heart failure and high-risk acute myocardial infarction. The authors concluded that there was no difference between ARBs and angiotensin-converting enzyme inhibitors in reducing all-cause mortality and hospitalisation for heart failure. The review was relatively well-conducted, although the authors did not consider differences in the dosages evaluated across the included studies.

Authors' objectives
To determine the efficacy of angiotensin-receptor blockers (ARBs) in patients with chronic heart failure and high-risk acute myocardial infarction (MI).

Searching
The Cochrane CENTRAL Register (Issue 3, 2003), the Cochrane Database of Systematic Reviews (Issue 3, 2003), CINAHL (1982 to November 2003), DARE (Issue 3, 2003), HealthSTAR (1975 to October 2003) and MEDLINE (from 1966) were searched for English language articles; the search terms were given. Additional studies were sought in the reference lists of selected trials and review articles, and through searches of abstracts from the 2002 and 2003 conference proceedings of the American College of Cardiology, the American Heart Association, the Canadian Cardiovascular Society, the European Society of Cardiology, and the Heart Failure Society of America.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with a duration of follow-up of at least 4 weeks were eligible for inclusion.

Specific interventions included in the review
Studies that compared ARBs with placebo or angiotensin-converting enzyme (ACE) inhibitors, or studies of combinations of ARBs and ACE inhibitors compared with ACE inhibitors alone, were eligible for inclusion. The ARBs evaluated in the included studies were losartan, candesartan, valsartan, eprosartan, irbesartan and telmisartan. The doses of these varied widely across the included studies. The duration of follow-up ranged from 4 weeks to 41 months.

Participants included in the review
Studies of participants with chronic heart failure or high-risk acute MI were eligible for inclusion. The mean age of the participants ranged from 54 to 73 years.

Outcomes assessed in the review
Studies that reported all-cause mortality or hospitalisation for heart failure were eligible for inclusion. Heart failure hospitalisation was defined as the number of patients with one or more post-randomisation admissions to hospital associated with heart failure, or for complications associated with the treatment of heart failure, or for the management of co-morbid conditions associated with heart failure.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Each study was assigned a quality score from 1 (lowest) to 5 (highest) using the Jadad instrument to assess
randomisation, blinding and the handling of withdrawals. The authors did not state how many reviewers performed the quality assessment.

**Data extraction**

Two reviewers independently extracted the data using a standardised form. Any disagreements were resolved through discussion and consensus, or by contacting the trial author. Data on the number of events of all-cause mortality and the number of participants requiring hospitalisation for heart failure were extracted from each study. If a study evaluated more than one dosage of the same treatment, the numbers of events were pooled for that individual study.

**Methods of synthesis**

How were the studies combined?
The results from the individual studies were combined in a meta-analysis. The random-effects model of DerSimonian and Laird was used in the presence of heterogeneity, otherwise the Mantel-Haenszel fixed-effect model was used. A pooled odds ratio (OR) and 95% confidence interval (CI) were calculated separately for all-cause mortality and heart failure hospitalisation. A funnel plot was used to assess publication bias.

How were differences between studies investigated?
Separate analyses were performed on studies that compared ARBs with placebo, ARBs with ACE inhibitors, and ARB and ACE inhibitor combinations with ACE inhibitors alone. Sensitivity analyses were performed on each group to investigate the influence of pre-specified end points on the results. Statistical heterogeneity was assessed using the chi-squared test (significance threshold, P=0.1). A cumulative meta-analysis was performed to investigate the robustness, over time, of all-cause mortality for the comparison of ARBs versus placebo.

**Results of the review**

Twenty-four RCTs (n=38,080) were included in the review.

Five studies scored 4 for methodological quality, 14 studies scored 3 and 5 studies scored 2.

Chronic heart failure.

ARBs were associated with significant reductions in both all-cause mortality (OR 0.83, 95% CI: 0.69, 1.00, P=0.048) and heart failure hospitalisations (OR 0.64, 95% CI: 0.53, 0.78, P<0.001) in comparison with placebo.

No significant difference was found between ARBs and ACE inhibitors for all-cause mortality (OR 1.06, 95% CI: 0.90, 1.26, P=0.48) or heart failure hospitalisation (OR 0.95, 95% CI: 0.80, 1.13, P=0.58).

No significant difference was found between combinations of ARB and ACE inhibitors and ACE inhibitors alone for all-cause mortality (OR 0.97, 95% CI: 0.87, 1.08, P=0.60). Combinations of ARB and ACE inhibitors were associated with a significant reduction in heart failure hospitalisations (OR 0.77, 95% CI: 0.69, 0.87, P<0.001).

No evidence of publication bias was found in studies that evaluated all-cause mortality in chronic heart failure.

High-risk acute MI.

Two studies compared ARBs with ACE inhibitors in patients with high-risk MI and found no significant difference in all-cause mortality (OR 1.14, 95% CI: 0.99, 1.13 and OR 0.97, 95% CI: 0.90, 1.06) or heart failure hospitalisation (OR 1.17, 95% CI: 0.98, 1.39 and 0.97, 95% CI: 0.87, 1.07).

**Authors’ conclusions**

There was no difference between ARBs and ACE inhibitors in reducing all-cause mortality and heart failure hospitalisation in patients with chronic heart failure and in those with high-risk acute MI. Therefore, ARBs could be considered a suitable alternative to ACE inhibitors.
CRD commentary
The review addressed a clear question and the inclusion criteria appeared appropriate. Several sources were used to identify relevant studies for inclusion, thus minimising publication bias. In addition, publication bias was formally assessed using a funnel plot. However, since inclusion was restricted to English publications, the possibility of language bias cannot be ruled out. It was unclear whether procedures were used to minimise bias when selecting studies for inclusion, but methods were used to minimise bias and error in the data abstraction process. The quality of the included studies was assessed systematically using appropriate methods.

Adequate details of each of the included studies and methods were given, suggesting differences in the doses of ACE inhibitors and ARBs across the included studies. Differences between the studies were explored in separate analyses and sensitivity analyses were performed to investigate the robustness of the results. However, the authors did not explore the influence of different doses of ARBs and ACE inhibitors on the efficacy of treatment. In summary, this was a relatively well-conducted review, although the authors’ conclusion would have been strengthened had the authors considered the different doses evaluated in the included studies.

Implications of the review for practice and research
Practice: ARBs should be considered a suitable alternative to ACE inhibitors in patients with chronic heart failure and high-risk acute MI.

Research: The authors stated that economic studies comparing ARBs with ACE inhibitors were sparse, and should consider safety and tolerability in addition to efficacy. The authors also emphasised the need to continually update meta-analyses.

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Other publications of related interest
This additional published commentary may also be of interest. Lee TH. Review: angiotensin receptor blockers do not differ from ACE inhibitors in chronic heart failure or acute MI. Evid Based Med 2005;10:76.

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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.