Angiotensin receptor blockers in heart failure: meta-analysis of randomized controlled trials


Authors' objectives
To determine the effect of angiotensin-receptor blockers (ARBs) on mortality and hospitalisation in patients with heart failure.

Searching
MEDLINE, EMBASE, Biological Abstracts, International Pharmaceutical Abstracts, Cochrane Controlled Trials Register, the Cardiovascular Randomized Clinical Trial (CVRCT) Registry, and the Science Citation Index were searched. The search dates covered 1966 to 2001 and the keywords were reported. Studies not published in full in peer-reviewed journals were excluded from the review.

Study selection
Study designs of evaluations included in the review
Blinded parallel-group randomised trials (RCTs) were eligible for inclusion. Crossover trials were excluded. All of the included studies were double-blind.

Specific interventions included in the review
Studies of ARBs versus placebo or angiotensin-converting enzyme inhibitors (ACEIs) were eligible for inclusion if treatment was given for at least 4 weeks. Studies were excluded if other investigational agents were co-administered without randomisation. Various regimens of eprosartan, losartan, valsartan, candesartan and ibresartan were used in the included studies. The mean duration of treatment was 4 weeks to 1.5 years.

Participants included in the review
Studies in patients with heart failure of New York Heart Association functional class II to IV were eligible for inclusion. In the included studies, 2 to 15% of the patients were in functional class IV and the mean age of the participants ranged from 56 to 73 years.

Outcomes assessed in the review
Studies that reported mortality or hospitalisation were eligible for inclusion. The primary outcome was all-cause mortality and the secondary outcome was hospitalisation for heart failure. The latter was defined as admission for worsening signs and symptoms or complications related to the treatment of heart failure, or syncope or arrhythmias related to acute exacerbations of heart failure.

How were decisions on the relevance of primary studies made?
The authors stated that relevant studies were determined by consensus.

Assessment of study quality
Study quality was assessed by the adequacy of randomisation, blinding, and descriptions of withdrawals and drop-outs. It appears that two reviewers independently assessed study quality.

Data extraction
Two reviewers independently extracted the data and any disagreements were resolved through consensus or a third reviewer. Investigators were contacted for missing information. Outcomes data were extracted to calculate the odds ratios (ORs) by intention-to-treat.

Methods of synthesis
How were the studies combined?
A meta-analysis was used to estimate the pooled OR with 95% confidence intervals (CIs). In the main analysis all the studies were combined using a random-effects model. Stratified analyses were then conducted for the following treatment comparisons: ARBs versus placebo, ARBs versus ACEIs, and ARB-ACEI combination therapy versus ACEIs. A fixed-effect model was used in the stratified analyses. ARB-ACEI combination therapy was analysed as ARB. If a study had more than one control arm these were combined. Publication bias was assessed using a funnel plot.

How were differences between studies investigated?
A chi-squared test was used to test for statistical heterogeneity in the meta-analyses. The stratified analyses were compared with the all-studies primary analysis to examine whether heterogeneity might be partly explained by differences in the type of control. Sensitivity analyses were conducted by excluding studies that included only ACEI-intolerant patients and studies that lasted less than 6 months.

Results of the review
Seventeen RCTs (n=12,469) were included.

When all the studies were pooled no difference was shown in all-cause mortality (OR 0.96, 95% CI: 0.75, 1.23). There was no difference in hospitalisation for heart failure based on 6 trials (OR 0.86, 95% CI: 0.69, 1.06). Statistical heterogeneity was of borderline significance in both of these analyses. There was a non-statistically significant trend towards lower mortality with ARBs versus placebo based on 7 trials (OR 0.68, 95% CI: 0.38, 1.22), but no difference between ARBs and ACEIs or between ARB-ACEI combination therapy and ACEIs. Only one large trial showed a statistically significant reduction in hospitalisation; this favoured the ARB-ACEI combination over ACEI. The sensitivity analyses excluding ACEI-intolerant patients and studies of less than 6 months did not change the findings. The funnel plot did not suggest the presence of publication bias.

Authors' conclusions
The authors concluded that in patients with symptomatic heart failure the results could not confirm that ARBs are better for reducing all-cause mortality or hospitalisation for heart failure, particularly compared to ACEIs.

CRD commentary
The review addressed a well-defined question. However, the restriction to peer-reviewed journal publications does not provide reassurance that all relevant data were included. The authors did attempt to minimise bias and errors in reviewing the studies selected for inclusion. The quality assessment appears to have been hindered by insufficient information on the primary studies, and to have led to an unproven assumption of adequate quality on the basis that the majority of the studies were multicentre trials. The characteristics of the individual studies, apart from quality, were presented clearly. Pooling appears to have been appropriate statistically, the contribution of individual trials to the pooled results was clear, and potential sources of heterogeneity were explored. The authors' conclusions were consistent with the strength of the evidence shown.

Implications of the review for practice and research
Practice: The authors stated that ARB monotherapy and ARB-ACEI combination therapy appear promising. However, evidence-based guidelines should continue to emphasise ACEIs as the primary therapy, although ARBs may be a reasonable substitute if ACEIs cannot be given.

Research: The authors stated that ongoing trials should help determine the role of ARBs in the treatment of heart failure. Three ongoing trials were named in the report: CHARM, OPTIMAL and VALIANT.

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