The effects of angiotensin-receptor blockers on mortality and morbidity in heart failure: a systematic review

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CRD summary
This review concluded that Angiotensin II receptor blockers did not show a beneficial effect on mortality when used in combination with ACE-I or when compared with ACE-I alone, but may have led to reductions in hospital admissions. Despite some methodological flaws and omissions, overall this was a reasonably well-conducted review and the authors’ conclusions are likely to be reliable.

Authors’ objectives
To evaluate the effect of angiotensin II receptor blockers on mortality and hospital admissions in heart failure patients.

Searching
English-language papers were identified through a search of MEDLINE from 1980 to 2007. Proceedings from major cardiology meetings from 2002 to 2007 were searched and references of retrieved articles were reviewed. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) of more than 500 patients with follow up of more than six months in patients with heart failure were eligible for inclusion. Trials were required to report mortality and/or hospital admission due to heart failure.

In the seven included trials, the angiotensin-receptor blockers (ARBs) studied were losartan (50mg daily), valsartan (160mg twice daily) and candesartan (32mg daily). Mean age of patients ranged from 63 to 74 years. Mean percentage of males ranged from 67% to 80%. Mean ejection fraction ranged from 27% to 35%. The most common cause of heart failure was ischaemic heart disease. Follow-up ranged from 43 to 164 weeks. Compliance to angiotensin-receptor blockers varied from 74% to 90% and for ACE-I varied from 70% to 85%.

The authors stated neither how papers were selected for review nor how many reviewers performed the selection. [A: Two independent reviewers selected papers for inclusion in the review.]

Assessment of study quality
Methodological quality was assessed by two independent reviewers using the Jadad scale (a 5-point scale of randomisation, allocation concealment, blinding and intention to treat analysis). Disagreements were resolved by consensus.

Data extraction
Data on numbers of events in each group were used to derive relative risks (RR) and 95% confidence intervals (CI) for dichotomous outcomes. Data were extracted by two reviewers. Disagreements were resolved by consensus with a third reviewer.

Data were stratified by two comparisons: angiotensin-receptor blockers plus angiotensin-converting enzyme inhibitors (ACE-I) compared to ACE-I; and angiotensin-receptor blockers compared to ACE-I

Methods of synthesis
The pooled RR and corresponding 95% CIs were calculated using the DerSimonian and Laird random-effects model. Statistical heterogeneity was assessed using the I² test (high values show increasing heterogeneity).

Results of the review
Seven trials (n=32,485, of which 27,495 had mortality data available) were included in the review. The median Jadad score was 4.

In chronic heart failure trials, there were no statistically significant differences on mortality when angiotensin-receptor blockers plus ACE-I were compared to ACE-I alone (RR 0.98, 95% CI 0.84 to 1.15, p=0.83; three trials) or when angiotensin-receptor blockers were compared to ACE-I (RR 0.95, 95% CI 0.56 to 1.62, p=0.86; three trials). Moderate heterogeneity was observed.

In trials that reported worsening heart failure-related hospitalisations, there was a statistically significant reduction in hospitalisation in patients randomised to angiotensin-receptor blockers plus ACE-I compared to ACE-I alone (RR 0.83, 95% CI 0.71 to 0.97, p=0.02; three trials). No differences were observed when angiotensin-receptor blockers were compared to ACE-I (RR 1.09, 95% CI 0.74 to 1.60, p=0.68; three trials). Statistically significant heterogeneity was observed for both comparisons.

In post-myocardial infarction trials, no significant differences in mortality were reported between patients randomised to angiotensin-receptor blockers compared to ACE-I (RR 1.05, 95% CI 0.97 to 1.14, p=0.19; two trials)

Authors' conclusions
Angiotensin II receptor blockers did not show a beneficial effect on mortality when used in combination with ACE-I or when compared with ACE-I alone, but may have led to reductions in hospital admissions.

CRD commentary
This review addressed a clear question supported by appropriate inclusion criteria. Only one electronic database was searched for studies and language restrictions were made, which may have led to publication bias. Publication bias did not appear to be considered in the report. Some efforts were made to retrieve unpublished data. Suitable methods were used in the data extraction and validity process to minimise risks of reviewer error and bias; it was unclear whether a similar approach was adopted when selecting studies. Validity assessment was carried out. Results were pooled appropriately using meta-analysis. Heterogeneity was assessed. Despite a limited search strategy and some omissions in the reporting of review methods, overall this was a reasonably well-conducted review and the authors conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that angiotensin-receptor blockers should be considered for reducing hospitalisations in patients with frequent visits to the hospital because of decompensation of heart failure following an economic analysis to more precisely evaluate the impact on the health care system.

Research: The authors stated that the role of angiotensin-receptor blockers in the secondary prevention of coronary events, cardiovascular and total mortality was being tested in RCTs.

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