The effect of renin-angiotensin system inhibitors on mortality and heart failure hospitalization in patients with heart failure and preserved ejection fraction: a systematic review and meta-analysis

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CRD summary
This review concluded that renin-angiotensin system inhibitors were not associated with reduced mortality or heart failure-related hospitalisations in patients with heart failure and preserved ejection fraction. Due to the possibility of missed trials, lack of reporting of review methodology and lack of quality assessment of included data, the authors' conclusions should be treated with caution.

Authors' objectives
To evaluate the effects of renin-angiotensin system inhibitors in patients with heart failure and preserved ejection fraction.

Searching
MEDLINE (1984 to 2008) and EMBASE (1990 to 2008) were searched. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that assessed the use of renin-angiotensin system inhibitors in patients with chronic symptomatic heart failure, with preserved left ventricular ejection fraction of 0.40 or more, were eligible for inclusion. Trials had to have follow-up of at least one year. The outcomes of interest were all-cause mortality and hospitalisation for heart failure.

In the included trials, the mean age of participants ranged from 67 to 75 years; 41 to 61% were women. Twenty-six to 79% of included patients had New York Heart Association (NYHA) Class III or IV heart failure; their mean left ventricular ejection fraction ranged from 54 to 64%. Aetiology of heart failure was ischaemic or hypertensive; some patients had hypertension, diabetes, atrial fibrillation, angina or had previous percutaneous coronary interventions or coronary artery bypass. Drugs assessed were irbesartan, candesartan and perindopril. Other concomitant drugs included diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, spironolactone, digoxin, nitrates or calcium channel blockers.

The authors did not state how the papers were selected for the review.

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

Data extraction
Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each trial.

Data were extracted by three (all) authors.

Methods of synthesis
Pooled odds ratios and 95% confidence intervals were calculated using a fixed-effect model. Heterogeneity was assessed using the Cochrane Q statistic.

Sensitivity analyses were carried out by removing one trial with higher symptom severity, limiting the results of one trial (with a high proportion of drop-outs at end of the trial) to one year follow-up, and including only the two largest trials.
Results of the review
Three RCTs were included in the review (8,001 patients). Mean follow up ranged from 26 to 50 months.

From 10 to 13% of patients were not taking the study drug at up to one year follow-up; 22 to 40% of patients were not taking the study drug at the end of the trial.

Compared with placebo, renin-angiotensin system inhibitors had no effect on all-cause mortality or heart failure related hospitalisations. There was no evidence of significant heterogeneity.

Results were similar for sensitivity analyses.

Authors’ conclusions
Renin-angiotensin system inhibition was not associated with any consistent reduction in mortality or heart failure-related hospitalisations in patients with heart failure and preserved ejection fraction.

CRD commentary
The aims of the review were clearly stated in terms of inclusion criteria for participants and intervention, but were less clear for study design as qualifications regarding trial sample size were not stated (although one smaller trial was excluded). The search was limited to two databases and did not appear to have included a search for unpublished studies, so publication bias could have affected the review. There was no mention of whether any language restrictions were applied, which made difficult to comment on any risk of language bias. It was not clear whether the methods of study selection were those aimed at reducing reviewer error or bias.

The quality of included trials was not assessed. The methods of synthesis appeared appropriate; heterogeneity was investigated.

Due to the possibility of missed trials, lack of reporting of review methodology and lack of quality assessment of included data, the authors’ conclusions should be treated with caution.

Implications of the review for practice and research
Practice: The authors stated that available evidence does not support routine prescribing of renin-angiotensin system inhibitors to patients with heart failure and preserved ejection fraction.

Research: The authors stated that new trials are needed to assess alternative mechanisms of renin-angiotensin system inhibitors in patients with heart failure and preserved ejection fraction. Subgroup analyses, using individual patient data from completed trials, are also needed to assess clinical outcomes.

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