Efficacy of ACE inhibitors in chronic heart failure with preserved ejection fraction: a meta analysis of 7 prospective clinical studies


CRD summary
This review concluded that in people with heart failure with preserved ejection fraction, angiotensin-converting enzyme inhibitors reduced all-cause mortality but had no effect on mortality from heart failure and rehospitalisation. The designs of the included studies were not entirely clear. Questions about the quality of included data and data synthesis methods mean that the conclusions may be unreliable.

Authors' objectives
To assess the efficacy of angiotensin-converting enzyme (ACE) inhibitors in people with chronic heart failure with preserved left ventricular ejection fraction (LVEF)

Searching
PubMed, EMBASE, BIOSIS, The Cochrane Library (Issue 3, 2009) database and the OVID platform were searched. Search terms were reported. Previous reviews and relevant references lists were checked. No language restrictions were applied.

Study selection
Prospective studies that assessed the effects of ACE inhibitors compared to placebo or other drugs in people with heart failure with preserved LVEF were eligible for inclusion. Follow-up needed to be at least six months in either study arm. Heart failure was defined by signs and symptoms and ejection fraction of at least 40%. The outcomes of interest were mortality (all-cause and due to heart failure), hospital readmission, six-minute walk distance and quality of life. People with heart failure following recent myocardial infarction or with heart transplant were excluded. Studies of fewer than 10 participants were excluded.

In the included studies, 58% of participants were women and mean ages ranged from 73 to 78 years. Aetiology of most participants was hypertension; in others it was heart failure, ischaemic heart disease, hypertensive heart disease and diabetes. Mean ejection fractions ranged from 40% or more to 50% or more. Participants with New York Heart Association (NYHA) class I-II heart failure comprised 11% to 78% and class III-IV from 21% to 89% of study populations. In two studies it was unclear what ACE inhibitors were used and in the other studies these included enalapril, quinapril, perindopril, lisinopril and ramipril. Comparators included placebo or no ACE inhibitor. In one study all participants received diuretics, in others concomitant treatments varied and included beta blockers, diuretics, calcium channel blockers and digoxin. Follow-up ranged from six to 60 months.

The authors did not state how many people performed the initial study selection. Full texts of selected papers were checked by two reviewers independently.

Assessment of study quality
Two reviewers independently assessed study quality using the Jadad scale. Disagreements were resolved by discussion.

Data extraction
Two reviewers independently extracted data to calculate odds ratios (ORs) and 95% confidence intervals (CI).

Methods of synthesis
Where there was no evidence of statistical heterogeneity and pooling was clinically appropriate, pooled odds ratios and 95% CI were calculated using a fixed-effect model; otherwise a random-effects model was used. Heterogeneity was assessed using X² test and I² statistic. Sensitivity analyses were used to investigate any effects of study quality and of the removal of one study. Subgroup analysis was undertaken based on age (>75 years and <75 years) and length of follow-up (>20.9 months and <20.9 months). Stratified analyses investigated length of follow-up (six, 12, 36 and 60 months). Publication bias was assessed using funnel plots and Egger's test.
**Results of the review**
Seven studies (2,554 participants, range 74 to 850) were included. Date of publication ranged from 1997 to 2008. Two studies scored 2 for quality and one each scored 3, 4, 5, 6 and 7. Tests showed no evidence of publication bias.

Compared to controls, ACE inhibitors were associated with a statistically significant reduction in all-cause mortality (OR 0.52, 95% CI 0.41 to 0.64; I²=18%; seven studies). Removal of one study resulted in a similar effect. Stratification according to length of follow-up showed similar results for all periods.

There was no statistically significant difference in death from worsening heart failure (I²=0%; three studies), heart failure related hospitalisation (I²=17%; four studies) and all-cause hospitalisation (I²=0%; three studies).

Subgroup analysis showed a beneficial effect on all-cause mortality for those less than 75 years old and at different follow-up times (>20.9 months and <20.9 months) and for heart failure-related hospitalisation in those more than 75 years old and at more than 20.9 months follow-up but not for other subgroups. Sensitivity analyses indicated no effect of study quality.

There was insufficient data available to meta-analyse results for quality of life and six-minute walk distance.

**Authors' conclusions**
In people with chronic heart failure with preserved ejection fraction, ACE inhibitors reduced all-cause mortality but had no effect on mortality due to heart failure or rehospitalisation.

**CRD commentary**
The aims of this review were clearly stated in terms of the inclusion criteria for participants and treatment but less clearly for study design. The search covered several relevant sources and was not limited by language. It was not clear whether unpublished studies were sought and it was possible that publication bias may have affected the review; authors' tests for publication bias were likely to be unreliable given the limited number of included studies. Methods aimed at reduced risks of reviewer error and bias were used during data extraction and quality assessment; methods for study selection were not clear. Quality was assessed but the scale used was designed for use with randomised controlled trials (RCTs) and the designs of the included studies were not clear; some studies may have been RCTs but others appeared to be observational studies. It was unclear what scores were considered of good and bad quality and which components of the assessment contributed to the scores. It may not have been appropriate to synthesis results by pooling data from studies of different designs. Tables indicated that results for quality of life were reported in most studies but were not presented.

Questions about the designs and quality of included studies and methods of data synthesis mean that the authors' conclusions may be unreliable.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that well designed prospective trials with comprehensive endpoints were needed to strengthen the understanding of ACE inhibitor therapy in people with heart failure with preserved LVEF.

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