Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients


Authors' objectives
To assess the effects of angiotensin-converting enzyme (ACE) inhibitors in patients with left ventricular dysfunction or heart failure using data from individual patients.

Searching
MEDLINE was searched for relevant trials of ACE inhibitors in acute MI (the search terms and dates were not reported). Researchers and colleagues in the pharmaceutical industry were consulted, and the reference lists from review articles were examined for other published or unpublished trials. The SOLVD trials were not part of the search strategy.

Study selection
Study designs of evaluations included in the review
The review included individual patient data (IPD) from randomised controlled trials (RCTs). Trials with more than 1,000 patients were eligible for inclusion. The average follow-up in the included trials ranged from 15 to 42 months.

Specific interventions included in the review
Studies of ACE inhibitors, where treatment was for 12 months at least, were eligible for inclusion. The included post-myocardial infarction (post-MI) studies compared captopril (12.5 mg initial dose, up to 25 to 50 mg three times daily), ramipril (2.5 mg twice daily initial dose, up to 5 mg twice daily for at least 6 months) and trandolapril (1 mg daily initial dose, up to 4 mg daily) with placebo. The timing of the first dose after MI ranged from 3 to 16 days in these trials, while the mean duration of treatment was 31 months (inter-quartile range: 19 to 41). Trials in patients with left-ventricular dysfunction (the SOLVD trials, see Other Publications of Related Interest no.1) compared enalapril (initial dose 2.5 or 5 mg twice daily up to 10 mg twice daily) with placebo. The timing of the first dose in the SOLVD trials was greater than one month.

Participants included in the review
Studies in post-MI patients were eligible for inclusion. These trials were compared with particular trials in patients with left-ventricular dysfunction (the SOLVD trials).

Outcomes assessed in the review
The outcomes assessed were: death; reinfarction; readmission for coronary heart failure; death or reinfarction; death or readmission for coronary heart failure; death or MI or readmission for coronary heart failure; stroke; and adverse events.

How were decisions on the relevance of primary studies made?
The trial investigators were contacted and invited to join a collaborative group. It may be assumed that the relevance of the included studies was checked with the investigators. The authors did not report any excluded studies.

Assessment of study quality
IPD sets from the included trials of ACE inhibitors in acute MI and the SOLVD trials were rigorously checked for completeness and consistency, and to check for agreement with the original publications. Queries concerning the validity of the included studies were resolved through communication with the principal investigators. The authors did not report any judgements relating to the excluded studies on the basis of validity.
Data extraction
The collaborative review group agreed on a common data set of 88 variables and specified these in a prospective protocol. IPD sets from each trial were sent to a coordinating centre. After checking, the data sets were incorporated into a master database. The variables presented in the review included age, gender, history (previous MI, diabetes, hypertension, smoker), clinical parameters, and the use of aspirin, diuretics and beta-blockers.

Methods of synthesis
How were the studies combined?
The Mantel-Haenszel method, as modified by Peto and Yusuf, was used to combine dichotomous variables across the different trials (see Other Publications of Related Interest nos.2-3). The standard quantity observed minus expected (O-E) was calculated for the number of events among treatment-allocated patients and controls. The variance of the total of the individual O-E z-values and the SD (square root of the variance) were calculated. For survival analyses and analyses involving regression principles, the data set was treated as if it came from one trial. The odds ratios (ORs) and 95% confidence intervals (CIs) were presented with corresponding two-sided p-values.

How were differences between studies investigated?
Standard statistical tests for heterogeneity were used to assess whether the results from the trials were significantly different from each other (details not reported). The outcomes were first analysed for the three MI trials separately from the SOLVD trials, and examined for consistency between the data sets. Data from all five trials were then combined.

Results of the review
Three RCTs (5,966 patients) in acute MI were included. These were compared with the two SOLVD trials (6,797 patients).

In the three post-MI trials, mortality was significantly lower with ACE inhibitors than with placebo (OR 0.74, 95% CI: 0.66, 0.83, p<0.0001). The results in the SOLVD trials were similar, with no apparent heterogeneity between the two categories of trials when the data were examined at the same time point. Pooling the post-MI trials and the SOLVD trials together showed fewer deaths with ACE inhibitors compared to placebo (OR 0.80, 95% CI: 0.74, 0.87, p<0.0001, n=12,763).

In the three post-MI trials, the rates of readmission for heart failure were lower with ACE inhibitors (OR 0.73, 95% CI: 0.63, 0.85, p<0.0001). The findings also favoured ACE inhibitors for the combined outcome of death or readmission for heart failure (OR 0.74, 95% CI: 0.67, 0.83, p<0.0001). The result was similar in all five trials combined (OR 0.74, 95% CI: 0.69, 0.80, p<0.0001).

Reinfarction in the three post-MI trials was lower with ACE inhibitors (OR 0.80, 95% CI: 0.69, 0.94, p<0.006). The SOLVD results were similar. Pooling all five trials gave an OR of 0.79 (95% CI: 0.70, 0.89, p=0.0001).

For the end point of death, infarction and readmission for heart failure, the overall OR was 0.72 (95% CI: 0.67, 0.78, p<0.0001). Thus, the treatment of 100 patients could prevent seven major events.

The benefits on all outcomes were independent of age, gender, and the baseline use of diuretics, aspirin and beta-blockers.

Stroke rates in the ACE inhibitor group and control groups were similar. A further analysis among patients with a history of hypertension or baseline systolic blood-pressure of 140 mmHg or higher did not reach statistical significance. Adverse event data were available from two post-MI trials and SOLVD. Hypotension and renal dysfunction were less common with ACE inhibitors (p<0.0001).

Authors' conclusions
ACE inhibitors lower rates of mortality, MI and hospital admission for heart failure in patients with left ventricular dysfunction or heart failure with or without a recent myocardial infarct.
CRD commentary
The inclusion criteria were stated for the intervention, participants and study design. It should be noted that only two particular trials in left ventricular dysfunction (the SOLVD trials) were included, i.e. the authors did not conduct a comprehensive search for other possibly relevant trials. The literature search to identify myocardial infarction trials was limited to one database, and the dates and search terms were not reported. An attempt was made to locate unpublished studies using appropriate sources. A prospective protocol was written before the data were collected, and the principal investigators of the included trials were invited to join a collaborative group to facilitate collection of IPD. The data were checked for validity using appropriate methods for IPD. The potential impact of the authors’ decision to exclude trials with less than 1,000 patients was not discussed, nor was there any mention of an attempt to identify how much data might exist in smaller trials and be missing from this analysis. In the analyses of events from which the reported ORs were derived, it was unclear what time points were used. Hazard ratios that take account of the whole follow-up period and censoring within each trial should have been reported. The survival analyses should not have treated the data as if they came from one trial.

The authors’ conclusions follow from the results presented. However, some aspects of the methodology are questionable, particularly the comprehensiveness of the search to identify relevant trials and the appropriateness of the analysis.

Implications of the review for practice and research
Practice: The authors state that the use of ACE inhibitors should be part of routine practice in patients with left ventricular dysfunction or heart failure with or without a recent myocardial infarct. Also, that they should be routinely used long-term in all eligible high-risk patients.

Research: The authors did not state any implications for further research.

Funding
Medical Research Council of Canada.

Bibliographic details

PubMedID
10821360

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Angiotensin-Converting Enzyme Inhibitors /therapeutic use; Female; Heart Failure /drug therapy /mortality; Humans; Male; Middle Aged; Randomized Controlled Trials as Topic; Survival Analysis; Treatment Outcome; Ventricular Dysfunction, Left /drug therapy /mortality
Accession Number
12000008280

Date bibliographic record published
31/05/2003

Date abstract record published
31/05/2003

Record Status
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.