Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure

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Authors' objectives
To evaluate the effect of angiotensin-converting enzyme (ACE) inhibitors on mortality and morbidity in patients with symptomatic congestive heart failure (CHF).

Searching
MEDLINE and other databases were searched, as well as reference lists of relevant articles. Correspondence was undertaken with other investigators and pharmaceutical companies in order to identify unpublished studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Results from the first half of crossover trials were included.

Specific interventions included in the review
Studies of ACE inhibitors compared with placebo used for at least 8 weeks were eligible for inclusion. The studies evaluated benazepril, captopril, cilazapril, enalapril, lisinopril, perindopril, quinapril and ramipril.

Participants included in the review
Studies of patients with symptomatic CHF were eligible for inclusion. Most of the patients in the included trials were classified as class II-III at entry using the New York Heart Association criteria. The ejection fraction at entry to studies ranged from less than 0.35 to less than 0.50.

Outcomes assessed in the review
Studies reporting mortality or major morbidity were eligible for inclusion. Total mortality, mortality due to specific causes (focus on cardiac mortality including progressive heart failure, sudden death, myocardial infarction, stroke), hospitalisation due to CHF, and thromboembolic events were assessed.

How were decisions on the relevance of primary studies made?
The authors did not state how the studies were selected for the review, or how many reviewers performed the study selection.

Assessment of study quality
There was no formal assessment of trial quality. The data collected from investigators were checked against published results.

Data extraction
The data were extracted by one reviewer and checked by either a second reviewer or with the trial investigator, where considered necessary. Investigators were also asked to complete standard data extraction forms. Any differences were resolved by discussion, or through correspondence with the investigators. Data were extracted on the incidence of mortality, hospitalisations, arrhythmic events, myocardial infarction, strokes, pulmonary emboli and other thromboembolic events.

Methods of synthesis
How were the studies combined?
The studies were combined using the Yusuf-Peto adaptation of the Mantel-Haenszel method and the DerSimonian and Laird random-effects method. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

How were differences between studies investigated?
Heterogeneity was investigated using the chi-squared statistic. Stratified analyses were performed for each agent and subgroup.

Results of the review
Thirty-four trials were identified, of which 32 were included in the meta-analysis (n=7,105).

Overall, 611 of the 3,870 patients allocated to an ACE inhibitors group (15.8%) and 709 of the 3,235 controls (21.9%) died (OR 0.77, 95% CI: 0.67, 0.88). Most of the benefit occurred in the first 90 days (OR 0.56, 95% CI: 0.44, 0.70, p<0.001; 32 trials). The benefit beyond 90 days was not statistically significant (OR 0.87, 95% CI: 0.75, 1.01; 12 trials).

Overall, 854 of the 3,810 patients on active treatment (22.4%) and 1,036 of the 3,178 patients on placebo (32.6%) died or were hospitalised for CHF (OR 0.65, 95% CI: 0.57, 0.74, p<0.001; 30 trials). The OR for CHF in the first 90 days of treatment was 0.53 (95% CI: 0.44, 0.63, p<0.001; 30 trials), and beyond 90 days was 0.76 (95% CI: 0.66, 0.88; 10 trials).

The most common cause of death was progressive heart failure, which was less frequent in the treatment group (OR 0.69, 95% CI: 0.58, 0.83, p<.001). Fatal and nonfatal myocardial infarction were significantly reduced in the treatment group (OR 0.80, 95% CI: 0.64, 0.99, p=0.04).

Death due to sudden or presumed arrhythmic events or myocardial infarction, and the incidence of strokes, pulmonary emboli or other thromboembolic events, were not statistically significant between groups.

The results of subgroup analyses were reported.

Authors' conclusions
Total mortality and hospitalisation for CHF are significantly reduced by ACE inhibitors, with consistent effects shown in a broad range of patients.

CRD commentary
The review addressed a clear question with well-defined inclusion criteria. It was unclear which databases were searched, however, trial investigators were contacted for unpublished data; the potential for publication bias is therefore unclear and was not investigated in the review. It was unclear whether language restrictions were applied during the searches, thus there is also the potential for language bias. It seems that data were obtained from both published sources and trial investigators. As the method of study selection was not described, the potential for selection bias cannot be assessed. It appears that not all of the data extraction was conducted in duplicate, thereby increasing the potential for errors. There was no formal assessment of trial quality, although data obtained from trialists were verified with published data. The lack of reporting of some of the review methods, and the potential for error and bias, make the reliability of the results uncertain.

Implications of the review for practice and research
Practice: The authors stated that there is persuasive evidence that ACE inhibitors should be used routinely and early in patients with CHF, especially those with a low ejection fraction.

Research: The authors emphasised the need to continue to explore additional, more effective means of treatment for patients with CHF.
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