Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review

Authors' objectives
To confirm or refute the theory that aspirin alters the effects of angiotensin-converting enzyme (ACE) inhibitor therapy on major clinical outcomes, by conducting a meta-analysis of individual patient data (IPD) from trials in which the patients were randomised to receive ACE inhibitors or placebo, and either took or did not take aspirin at baseline.

Searching
MEDLINE was searched, although the dates over which the search was conducted were not given. In addition, researchers and colleagues in the pharmaceutical industry were contacted, and reference lists from review articles were scanned (see Other Publications of Related Interest no.1). Principal investigators from each of the large randomised trials (short- and long-term) of ACE inhibitors in MI and the Studies of Left Ventricular Dysfunction (SOLVD) trials were invited to form the ACE-Inhibitor Myocardial Infarction Collaborative Group, which agreed on the data to be collected, and to review the analyses and manuscripts.

Study selection
Study designs of evaluations included in the review
The review included IPD from randomised controlled trials with more than 1,000 patients and with a follow-up of more than 1 year.

Specific interventions included in the review
ACE inhibitors versus placebo controls. The ACE inhibitors used were enalapril (up to 10 mg twice daily; 2 trials), captopril (up to 50 mg three times daily), ramipril (up to 5 mg twice daily, or up to 10 mg once daily; 2 trials) andtrandopril (up to 4 mg once daily). In addition, the patients took or did not take aspirin at baseline (dosages not given); this use of aspirin was not random.

Participants included in the review
The included patients were those diagnosed with left ventricular dysfunction with or without myocardial infarction (MI), those with coronary artery disease, or those with clinical heart failure post-MI.

Outcomes assessed in the review
The outcome definitions differed between the original trials and were retained in the review. The primary outcome was a composite of all of these. The outcomes included death, MI, stroke, hospital admission for congestive heart failure, and revascularisation.

How were decisions on the relevance of primary studies made?
Any queries were resolved by communication with the principal investigators.

Assessment of study quality
The collaborative group agreed a prospective protocol for data collection that summarised the methods, pre-specified analyses and a common data-set of 88 variables (see Other Publications of Related Interest no.1). The data sets were rigorously checked for completeness and consistency to ensure no errors occurred during reformatting, and for agreement with the original publications. Any queries were resolved with the principal investigators.

Data extraction
The data sets from each trial were checked for completeness and consistency before being incorporated into a master
database for analysis. The baseline characteristics included age, gender, heart rate, blood-pressure, previous MI, diabetes, hypertension, whether currently smoking, and prescribed diuretics or beta-blockers. The outcomes are listed above (see 'Outcomes Assessed in the Review' field).

**Methods of synthesis**
How were the studies combined?
The odds ratios (ORs) with 99% confidence intervals (CIs), to allow for multiplicity of effects, were calculated for each trial in an intention-to-treat analysis. They were then pooled using the Mantel-Haenszel method, as modified by Yusuf et al. (see Other Publications of Related Interest no.2).

How were differences between studies investigated?
Standard tests of heterogeneity were used to find significant differences between the trials. Interactions were tested using logistic regression.

**Results of the review**
Six double-blind randomised trials with 22,060 patients were included. A total of 14,410 patients received aspirin; the mean age was 64 years (standard deviation, SD=9) and 21% were women. A total of 7,650 patients did not receive aspirin; the mean age was 62 years (SD=10) and 25% were women.

Differences in the baseline characteristics of the aspirin and no-aspirin subgroups were found, and these varied between the trials. A significant difference (p=0.01) between the proportional reductions in risk with ACE inhibitor therapy was found only for MI with aspirin (OR 0.86, 99% CI: 0.75, 0.99) versus no-aspirin (OR 0.66, 99% CI: 0.54, 0.81). In the primary (composite) outcome, the test for aspirin interaction showed a weak trend (p=0.07) for reduced benefit from aspirin (OR 0.80, 99% CI: 0.73, 0.88) versus no-aspirin (OR 0.71, 99% CI: 0.62, 0.81).

**Authors' conclusions**
There is only weak evidence of a reduction in benefit when aspirin is added to ACE inhibitor therapy. Both treatments have been shown to be beneficial separately, therefore, both should be used concomitantly in high-risk patients in the absence of clear contraindications.

**CRD commentary**
This IPD meta-analysis asked a clear question that had been posed in a subgroup analysis in the authors' earlier review (see Other Publications of Related Interest no.1). The search strategy and analysis used previously were reasonably comprehensive, despite being limited to a single database and not including any trial registers; it was updated for the present review. The authors did not achieve their stated aim of confirming or refuting the hypothesis of a reduced benefit from ACE inhibitors when aspirin is given concomitantly.

**Implications of the review for practice and research**
Practice: The authors state that aspirin and ACE inhibitors should be prescribed together in high-risk patients.

Research: The authors state that the least biased assessment of the possibility of interactions would involve a very large randomised 2x2 factorial trial of aspirin versus placebo, and ACE inhibitors versus placebo. However, they say that such a trial is improbable on ethical and statistical grounds. Both treatments have been shown to be beneficial, and a substantial reduction in risk was still apparent when they were combined.

**Bibliographic details**
Other publications of related interest

This additional published commentary may also be of interest. Cohn JD. Review: concomitant aspirin use does not reduce the effectiveness of ACE inhibitors. ACP J Club 2003;138:64.

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Record Status
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