Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina: a meta-analysis

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Authors' objectives
To determine whether treatment with intravenous heparin and aspirin is more effective than treatment with aspirin alone, in preventing myocardial infarction (MI) or death in patients with unstable angina.

Searching
MEDLINE was searched from January 1966 to September 1995 for articles published in any language using the keywords 'aspirin', 'heparin' and 'unstable angina'. Additonal material was obtained by handsearching of references from identified articles, and by consultation with experts.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) comparing intravenous heparin and aspirin with aspirin alone. MI was confirmed by prolonged chest pain and ECG or biochemical changes.

Specific interventions included in the review
Intravenous heparin and aspirin.

Participants included in the review
Patients admitted to hospital with the diagnosis of unstable angina or non-Q-wave MI. Patients with evolving Q-wave MI on admission, coronary artery bypass grafting within 12 months prior to admission, a contraindication to aspirin or anticoagulation, or had already been anticoagulated at admission, were excluded.

Outcomes assessed in the review
The primary outcomes were incidence of MI or death during randomisation. Secondary outcomes were incidence of ischaemic pain and major bleed, and MI, death or revascularisation during the 12 weeks following randomisation.

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

Assessment of study quality
Patient selection, blinding, drop-out and withdrawal rates, adequacy of randomisation. Two reviewers independently assessed each study, and any discrepancies were settled by discussion.

Data extraction
Two reviewers independently assessed each study, one blinded and one unblinded to journal, year of publication, authors and institution. Any discrepancies were settled by discussion.

Methods of synthesis
How were the studies combined?
The odds ratios of the treatment effects were estimated using the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest).

How were differences between studies investigated?
A chi-squared test for heterogeneity was undertaken. Formal statistical tests were performed to look at interactions between MI, treatment regime and study. Differences in quality characteristics (blinding, follow-up, randomisation) were examined. A sensitivity analysis was also performed, excluding one study with a very high death rate.

**Results of the review**

Six RCTs with 1,353 patients were included. In one study heparin was administered as intermittent intravenous boluses, while in the other 5 studies heparin was continuously infused.

The summary relative risk (RR) of MI or death during randomised treatment for patients with aspirin plus heparin, compared to those with aspirin alone, was 0.67 (95% confidence interval, CI: 0.44, 1.02, p=0.06); heterogeneity was non significant (p=0.78). In the 4 studies that reported it, the summary RR of MI or death after discontinuation, and up to 12 weeks after randomised treatment, was 0.82 (95% CI: 0.56, 1.20) for patients with aspirin plus heparin, compared to those with aspirin alone; heterogeneity was non significant (p=0.76). No statistical differences were found for all other outcome measures. To look for possible publication bias, the correlation (r) between the RR estimate and sample size was calculated and found to be non significant (r=0.25, p=0.64).

**Authors' conclusions**

Unless heparin is contraindicated, most patients with unstable angina should be treated with both aspirin and heparin.

**CRD commentary**

This is a well-written thorough review. The search was restricted to MEDLINE and, therefore, might have missed studies. It is not stated in the authors' objectives that the primary outcome was MI or death during randomised treatment. By insisting on death data during the duration of randomised treatment, relevant studies may have been excluded. Further, details from one trial on which the regime was unclear could have been obtained from the authors. By reporting death during active treatment separately from follow-up period, an artificially inflated impression of the potential usefulness of the therapy was obtained. No information is given on follow-up of longer than 12 weeks, which may have been available from the studies.

**Implications of the review for practice and research**

If the excluded studies do not answer the posed question, a major trial with longer follow-up is required before clinical recommendations can be made. A review of studies and possibly further research of the use of low molecular weight heparin might be indicated. An economic evaluation would be useful.

**Bibliographic details**


**PubMedID**

8769591

**Other publications of related interest**


**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Angina, Unstable /drug therapy /mortality /therapy; Angioplasty, Balloon, Coronary; Aspirin /administration & dosage /therapeutic use; Drug Therapy, Combination; Hemorrhage; Heparin /administration & dosage /therapeutic use;
Humans; Incidence; Infusions, Intravenous; Likelihood Functions; Linear Models; Logistic Models; Myocardial Infarction /epidemiology /prevention & control /therapy; Myocardial Revascularization; Partial Thromboplastin Time; Randomized Controlled Trials as Topic; Recurrence; Risk; Survival Rate

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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.