Authors' objectives
To determine the effect of early anticoagulation on the mortality and other major clinical events in patients with suspected acute myocardial infarction (MI), and to assess the effect of adding heparin to aspirin.

Searching
A formal computer-aided literature search was undertaken. Additional materials was located by examining reference lists, and by contacting other investigators and pharmaceutical companies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs). A study was included if the trials were considered unconfounded, defined as comparing the effect of a standard treatment with and without anticoagulant therapy. Trials were excluded if they were not truly randomised, or if they compared one anticoagulant regime with another. The average follow-up period was 10 days.

Specific interventions included in the review
Low-dose heparin (10,000 to 15,000 IU/day) without other antithrombotic therapy, high-dose heparin (more than 20,000 IU/day) without other antithrombotic therapy, high-dose heparin plus oral anticoagulants, high-dose heparin plus aspirin, and aspirin alone; heparin was given subcutaneously or as an intravenous bolus. Therapy included fibrinolytic therapy or no fibrinolytic therapy. Therapy was started at varying times after admission (from less than 4 to less than 72 hours) and was continued from 1 to 28 days.

Participants included in the review
Patients with suspected acute MI admitted to hospital were included.

Outcomes assessed in the review
The outcomes were death, reinfarction, stroke, pulmonary embolism, venous thrombosis (detected by radio-labelled fibrinogen or venogram), and major bleeding (requiring transfusion).

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
Validity was assessed on the basis of blinding. The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
The odds reduction was calculated separately for each trial. Adjusted totals were calculated after conversion of any unevenly randomised trials to even ones, by counting control groups more than once. The stratified odds ratio (heparin; control) was used for combinations of individual trials for a particular anticoagulant regime.

How were differences between studies investigated?
A standard chi-squared test for heterogeneity was used to assess heterogeneity between differing heparin doses in trials of heparin, and to assess the heterogeneity of effect between trials with and without aspirin for different outcome measures. Sensitivity analysis was performed on the incidence of pulmonary embolism after excluding non-blinded trials.

Results of the review
Twenty-six RCTs from 1960 to 1994 (73,000 patients) were identified. Low-dose heparin in the absence of other antithrombotics: 7 trials from 1972 to 1989 (807 patients). High-dose heparin without other antithrombotics: 8 trials from 1960 to 1990 (1,678 patients). High-dose heparin plus oral anticoagulants without other antithrombotics: 6 trials from 1972 to 1987 (2,592 patients). High-dose heparin in presence of aspirin: 6 trials from 1987 to 1994 (68,090 patients).

Heparin in the absence of aspirin: a 25% (95% confidence interval, CI: 10, 38, 2P=0.002) proportionate reduction in mortality in patients allocated to heparin treatment was found. There was a non significant difference in reinfarction rates between treatment groups.

Proportionate reduction in stroke in the heparin treatment group: 49% (approximate 95% CI: 33, 67, 2P=0.01).

Reduction in pulmonary embolism in the heparin group: 51% (approximate 95% CI: 33, 67, 2P<0.001).

The analysis was repeated after excluding trials where knowledge of the treatment group may have influenced assessment of pulmonary embolism; a similar reduction was observed.

The reporting of bleeding was stated to be incomplete: in trials of high-dose heparin there was a doubling of the risk of a major noncerebral bleed (31 out of 1,322 versus 14 out of 1,321 patients; 2P=0.01).

None of the above showed statistically-significant heterogeneity between heparin regimes.

Heparin in the presence of aspirin: a 6% proportionate reduction in death was found in the heparin group (95% CI: 0, 10, 2P=0.03). The reduction was smaller than that seen in the absence of aspirin (chi-squared=5.82, P<0.05).

Adding heparin to aspirin produced no additional reduction in strokes compared to aspirin alone.

There was a 50% increase in the odds of having a major bleed reported in the heparin plus aspirin group, compared to the aspirin group (1 versus 7%; 2P<0.001).

Authors' conclusions
There is at present little evidence from randomised trials of any significant, further net clinical benefit from adding either subcutaneous or intravenous heparin to the treatment of patients who are given aspirin.

CRD commentary
Details of the databases searched were not given, so it is not possible to comment on the likelihood of omitted studies. The criteria used to define terms in the primary studies such as 'suspected acute myocardial infarction' and outcomes such as 'reinfarction, stroke, pulmonary embolism' were not stated, and these outcomes were not assessed blind to treatment group. The dose of aspirin used in the trials was not mentioned. The influence of changing medical practice over time is discussed with respect to the lower rate of pulmonary embolism in this study than previous. The relevance of a variable time lag between admission or the critical event and the commencement of therapy is unknown. Mortality results over a longer follow-up period (2 trials) were only mentioned briefly in the discussion section.
Implications of the review for practice and research

There is no good evidence to support the continued addition of heparin to aspirin therapy in the routine treatment of patients with MI.

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