Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis

Authors' objectives
To assess the effect of unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) in acute coronary syndrome without ST elevation (unstable angina and non-Q-wave myocardial infarction).

Searching
The authors searched the electronic databases of MEDLINE and EMBASE (dates not provided) using a combination of search terms related to heparin and acute coronary syndrome without ST elevation. The authors also made informal searches for studies known to colleagues and made searches of the reviewers' personal files. Reference lists of published papers were also scanned and experts in the field were canvassed as a source of unpublished trial results.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs). Trials where there was a lack of clarity regarding randomisation were excluded.

Specific interventions included in the review
Unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) compared with placebo or untreated control, or comparing UFH with LMWH. Trials of aspirin versus heparin, and heparin plus aspirin versus non-aspirin control or heparin versus non-aspirin control were excluded. Trials were either short-term (up to 7 days) or long-term (up to 3 months) in duration.

Participants included in the review
Aspirin-treated patients diagnosed with acute coronary syndrome without ST elevation (e.g. unstable angina, non-Q-wave myocardial infarction). In the included studies, the mean age of patients ranged from 57-70 years, and the percentage of men ranged from 58% to 100%.

Outcomes assessed in the review
Major bleeding and a composite outcome of death and myocardial infarction (MI).

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 reviewers performed the selection.

Assessment of study quality
No formal assessment of quality was undertaken.

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

Data were extracted for the categories of: Study identification and year of publication, number of participants, mean age (years), sex (% male), eligibility after pain onset (hours), intervention for treatment group and control group (broken out into short-term and long-term), duration of treatment, and primary efficacy outcome.

When data were incomplete, additional details were requested by correspondence, usually with the principal investigator.
Individual ORs and 95% CIs were calculated for the individual studies.

**Methods of synthesis**

How were the studies combined?
Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using a modification of the Mantel-Haenszel method.

How were differences between studies investigated?
Trials were examined for heterogeneity by dividing them into strata based on the primary comparison and treatment period. The chi-square statistic was used to test for heterogeneity.

**Results of the review**

Twelve RCTs were included in the review with 17,157 participants.

Six RCTs (1,353 participants) reviewed short-term UFH versus placebo or untreated control.

Two RCTs (1,639 participants) reviewed short-term LMWH versus placebo or untreated control.

Five RCTs (12,171 participants) reviewed short-term LMWH versus UFH.

Five RCTs (12,099 participants) reviewed long-term LMWH versus placebo.

The pooled OR for MI or death during short-term (up to 7 days) UFH compared with placebo or untreated control was 0.67 (95% CI: 0.45, 0.99; p = 0.045), without statistical heterogeneity (chi-square = 2.90, p = 0.82).

The pooled OR for MI or death during short-term (up to 7 days) LMWH compared with placebo or untreated control was 0.34 (95% CI: 0.20, 0.58; p < 0.0001). There was no report of heterogeneity for this result.

The pooled OR for MI or death during short-term (up to 7 days) UFH or LMWH compared with placebo or untreated control was 0.53 (95% CI: 0.38, 0.73; p = 0.0001) or 29 events prevented per 1,000 patients treated. There was no statistical evidence of heterogeneity (chi-square = 6.52, p = 0.37). The pooled OR for MI or death during short-term (up to 7 days) LMWH compared with UFH was 0.88 (95% CI: 0.69, 1.12; p = 0.34) which was not statistically significant. There was no statistical evidence of heterogeneity (chi-square = 4.49, p = 0.49). The pooled OR for MI or death during long-term (up to 3 months) LMWH compared with placebo or untreated control was 0.98 (95% CI: 0.81, 1.17; p = 0.80) which was not statistically significant. Statistical heterogeneity test not reported. Long-term LMWH was associated with a significantly increased risk of major bleeding (OR 2.26, 95% CI: 1.63, 3.14; p < 0.0001) which is equivalent to 12 major bleeds per 1,000 patients treated.

**Authors' conclusions**
The authors state that in aspirin treated patients with acute coronary syndrome without ST elevation, short-term UFH or LMWH halves the risk of MI or death. There is no convincing evidence in efficacy or safety between LMWH and UFH. Long-term LMWH has not been proven to confer benefit additional to aspirin and there is no evidence to support its use after the first 7 days.

**CRD commentary**
The authors have clearly stated the research question and inclusion and exclusion criteria. The literature search is limited to only two databases and does not report search dates or language restrictions. It does, however, include searches for unpublished and grey literature. The quality of the included studies was not formally assessed and the authors have not reported how the articles were selected, or who performed the selection and the data extraction.

The data extraction is reported in tables and discussed in the text of the review. The studies were combined in a statistical meta-analysis and there were tests for heterogeneity.
The conclusions stated by the authors appear to follow from the results but should be viewed with caution because of the lack of validity assessment and information regarding the process of the review which may have introduced bias.

Implications of the review for practice and research
The authors did not state any implications for further research and practice.

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