Low-molecular-weight heparins in the management of acute coronary syndromes
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Authors' objectives
To evaluate the role of low-molecular-weight heparins (LMWH) in the management of patients with unstable angina or non-Q-wave myocardial infarction.

Searching
The authors searched for English language publications using the MEDLINE electronic database (1966 to December 1998). The search terms used in the search were: ‘unstable angina’, ‘myocardial infarction’, ‘heparin’, and ‘low-molecular-weight heparin’. The authors also searched the bibliographies of retrieved studies for additional relevant studies and contacted experts in the field to obtain information on unpublished results and conference abstracts.

Study selection
Study designs of evaluations included in the review
Randomised, controlled clinical trials (RCTs), and open labelled dose-ranging studies which reported efficacy or safety outcomes.

Specific interventions included in the review
Low-molecular-weight heparins (LMWH) including enoxaparin (1.0 mg/kg SC BID or 30 mg IV bolus then 1.0 mg/kg SC BID), dalteparin (120 U/kg SC BID), and nadroparin (0.1 mL/10kg SC BID), versus unfractionated heparin (UFH) or placebo.

Participants included in the review
Patients with unstable angina or non-Q-wave myocardial infarction.

Outcomes assessed in the review
Total events at 7 days (recurrent angina at 7 days, acute myocardial infarction (MI) at 7 days, revascularisation at 7 days or death at 7 days); death/MI at 6 or 14 days; death/MI/angina at 6-45 days; major hemorrhage at 14 days; death/MI/urgent revascularisation at 8 days; cardiovascular death/MI/refractory angina at 14 days.

How were decisions on the relevance of primary studies made?
All trials were evaluated independently by all of the authors for inclusion in the review.

Assessment of study quality
The authors do not report a method for assessing validity. All trials were evaluated independently by all of the authors for scientific validity.

Data extraction
The authors do not state who, or how many of the reviewers, performed the data extraction.

Data were extracted on trial identification, patient characteristics, treatment, control, and primary end-points for each included trial.

Methods of synthesis
How were the studies combined?
The studies were combined in a qualitative narrative presentation of the data.
How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Six RCTs and 1 open-labelled dose ranging study were included in the review with 14,386 participants.

The narrative results of the seven included studies are listed individually below:

1. There was a significant reduction in the number of patients reaching the primary end point of recurrent angina, nonfatal MI, urgent revascularisation, or death in the nadroparin group compared with the UFH and placebo groups. Patients receiving nadroparin had significantly less recurrent angina than the patients in the UFH or placebo groups. There was no significant difference in major bleeding complications, however, more patients in the UFH group experienced minor bleeding. There was a trend toward favourable results using nadroparin to prevent MI and the need for revascularisation, but the sample size was insufficient to conclusively evaluate this end point.

2. Results after 6 days indicated a 63% reduction in the primary end point of death or MI in the dalteparin group compared with the placebo group. The absolute risk reduction of 3% correlates to 1 death or MI prevented at 6 days for every 34 dalteparin-treated patients. The difference between the 2 groups was not significant when evaluated at 40 and 150 days. The dalteparin-treated groups experienced more minor bleeding complications.

3. At 6 days there was no significant difference between the 2 groups in reaching the same composite triple end point. There was no difference in major and minor bleeding complications between the 2 groups. The authors concluded that dalteparin seemed to be equivalent to UFH in the acute phase of unstable angina or non-Q-wave MI, and that prolonged administration of a reduced dose of dalteparin offered no advantage over long-term therapy with aspirin alone. The trial was not powered to detect a difference in death, MI, or recurrent angina during the acute phase.

4. The primary end point was major hemorrhage occurring within 2 weeks of enrolment, which occurred more frequently in patients receiving 1.25 mg/kg of enoxaparin than in the 1.0 mg/kg group. No difference was found in any of the secondary end points of death, MI or recurrent ischemia requiring revascularisation. Since this trial was an unblinded dose-ranging study, no definitive conclusions could be made about the efficacy of enoxaparin in unstable angina.

5. At the conclusion of the trial, significantly fewer enoxaparin-treated patients reached the primary end point of death, nonfatal MI, or recurrent angina at 14 days. This significant difference was maintained at 30 days. There was no difference between groups at 48 hours, nor was there a difference in the combination end point of death or MI at 14 and 30 days. Results after 1 year of follow-up have been presented, and the early benefit of enoxaparin in the primary end point was maintained (32% for enoxaparin versus 35.7% for UFH; P = 0.02). There was no difference between the groups in major bleeding complications; however more patients in the enoxaparin groups experienced minor bleeding.

6. Results indicate that fewer enoxaparin-treated patients reached the primary end points of death, nonfatal MI, and severe recurrent ischemia requiring revascularisation during the acute phase. This initial benefit was maintained at 43 days, however no relative reduction on events occurred during the chronic phase. Superiority of enoxaparin in the acute phase was not associated with any increase in major bleeding, however there was an increase in major hemorrhage during the chronic phase.

Combined analysis of trials 5) and 6) showed a consistent reduction in the odds of the triple end point of death, MI, or urgent revascularisation at 8, 14, and 43 days after randomisation. Overall, there was a relative 20% reduction at 43 days (OR = 0.80, 95% CI: 0.71, 0.91). This reduction was also evident when the double end point of death or MI was evaluated at 43 days (OR = 0.82, 95% CI: 0.69, 0.98).

7. Results indicated no significant difference in the primary end point between the 3 treatment groups for cardiovascular death, MI, or refractory or recurrent angina at 14 days, with event rates of 17.8%, 20.0%, and 18.1% respectively. Major bleeding was similar between the groups when evaluated at 6 days, however a higher major bleeding rate occurred in the 14-day nadroparin arm compared with the 6-day nadroparin and UFH groups (3.5%, 1.5%, and 1.6% respectively) when evaluated at 14 days.
Cost information
One trial found that the improved clinical outcomes for patients treated with enoxaparin were associated with a cost saving. Despite the US $75 incremental drug cost of administering enoxaparin rather than UFH, cost savings of US $763 were realised at hospital discharge and US $1172 at 30 days.

A Canadian study found that the average cost per patient in Canada for enoxaparin was determined to be Canadian $848 versus Canadian $892 for UFH.

Authors’ conclusions
The authors state that LMWHs are superior to placebo and UFH in reducing ischemic events or death in the acute phase of unstable angina or non-Q-wave myocardial infarction. Prolonged therapy with lower doses of LMWHs may not offer any advantage over aspirin in the prevention of coronary events of death.

Major bleeding complications are similar for LMWHs and UFH, but minor bleeding complications are more common with LMWHs primarily because of injection-site hematomas. Finally, LMWHs appear to be cost-effective compared with UFH based on pharmacoeconomic analyses conducted in Canada and the United States based on the results from two studies. Taken together, the use of LMWHs for the treatment of unstable angina or non-Q-wave myocardial infarction should be favoured over UFH.

CRD commentary
The authors have clearly stated their research question but not the inclusion and exclusion criteria. The literature search appears thorough, however the authors may have missed studies published outside the United States by restricting the searches to MEDLINE and by restricting the search to English language publications. The authors also do not mention the inclusion of unpublished data in the review. The quality of the included studies was not assessed and the authors have not reported on how the articles were selected, or how many of the reviewers were involved in the data selection and extraction.

The data extraction is reported in tables and text. The data was presented in a narrative discussion listing results without a synthesis of the data. There were no tests for heterogeneity but the authors have discussed some of the methodological and data limitations in the review. The authors conclusions appear to follow from the results but these should be viewed with caution because of the stated methodological limitations of the review.

Implications of the review for practice and research
Practice: The authors state that, based on the best available evidence, a class effect of LMWH should not be assumed, and enoxaparin should be the preferred LMWH agent for patients with unstable angina or non-Q-wave MI. Enoxaparin, 1.0 mg/kg, subcutaneously twice daily should be continued for at least 72 hours, but not beyond the hospital phase.

Research: The authors do not state any implications for further research.

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