Use of low-molecular-weight heparins in the management of acute coronary artery syndromes and percutaneous coronary intervention

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CRD summary
This review compared the effectiveness of low molecular weight heparins (LMWHs) with unfractionated heparin for the treatment of acute coronary syndromes, and as an adjunct to percutaneous coronary intervention (PCI). The authors concluded that LMWHs could potentially replace unfractionated heparin as the antithrombotic treatment of choice across the spectrum of acute coronary syndromes, and may also be effective for PCI. Since the review methodology was unclear and could be subject to many biases, the authors' conclusions may not be robust.

Authors' objectives
To assess the efficacy and safety of low molecular weight heparins (LMWHs), in comparison with unfractionated heparin (UFH), across the spectrum of acute coronary syndromes (ACS) and as an adjunct to percutaneous coronary intervention (PCI).

Searching
MEDLINE was searched from 1990 to 2001; the MeSH terms were given. Further studies were identified by reviewing reference lists, and conferring with experts and pharmaceutical companies. Abstracts from relevant annual meetings were also reviewed.

Study selection
Study designs of evaluations included in the review
To assess interventions undertaken in patients with STEMI and UA/NSTEMI, randomised controlled trials (RCT) were eligible for inclusion. To assess interventions in the PCI setting, RCTs, registries examining clinical outcomes, and pharmacodynamic and/or pharmacokinetic studies were eligible for inclusion

Specific interventions included in the review
Studies that compared LMWHs against either UFH or placebo were eligible for inclusion. The specific interventions assessed in the review were dalteparin alone or in combination with abciximab, UFH, nadroparin, enoxaparin alone or in combination with glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban), and LMWHs in combination with fibrinolytic therapy.

Participants included in the review
Participants with ST-segment elevation myocardial infarction (STEMI), unstable angina (UA)/non-ST-segment elevation MI (NSTEMI), and those undergoing elective or urgent PCI, were eligible for inclusion. Specific details of the included patients were not available.

Outcomes assessed in the review
No inclusion criteria were specified in relation to the outcome measures. The outcomes assessed were a composite of death, reinfarction or recurrent angina, or patency and flow rates.

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

Assessment of study quality
The authors stated that data quality was determined by publication in a peer-reviewed journal, or by presentation at an official cardiology society-sponsored meeting. No further formal validity assessment was undertaken.
**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted on the number of participants, intervention, duration of follow-up, the primary efficacy outcome, adverse bleeding events, and the timing of both efficacy and safety outcomes.

**Methods of synthesis**

**How were the studies combined?**
The studies were grouped by the type of participants, and combined in a narrative.

**How were differences between studies investigated?**
Differences between the studies were discussed in relation to the different interventions.

**Results of the review**
The authors stated that 31 RCTs were included in the review. The number of participants was unclear.

**Non-ST-elevation ACS (UA/NSTEMI).**

Differences in trial design, patient selection and characteristics of the preparations made comparisons among LMWHs difficult. One trial had compared the two LMWHs enoxaparin and tinzaparin. The composite primary end point (death, reinfarction or recurrent angina) was significantly lower with enoxaparin than with tinzaparin at day 7 (12.3% versus 21.1%). This difference persisted at 30 days, but was driven almost entirely by a reduction in recurrent angina. Major bleeding was uncommon and not significantly different between the two treatment groups.

**Initial medical management of ACS.**

The combination of LMWH and glycoprotein IIb/IIIa inhibitors was assessed in 5 trials. The results showed that major haemorrhage occurred rarely in the LMWH and glycoprotein IIb/IIIa treatment arms (0.3% to 1.8%). In addition, no increase in bleeding was noted in patients who proceeded to PCI.

**Duration of therapy with LMWH in ACS.**

No additional benefit, above that observed in hospital, was shown beyond discharge among patients with ACS. In addition, an increase in bleeding with prolonged LMWH treatment was observed.

**STEMI.**

Eight trials assessed LMWH with fibrinolytic therapy in STEMI. Infarct-related arterial patency following fibrinolytic therapy was reported in 3 trials. The use of adjunctive LMWH resulted in improved late coronary artery patency rates and a tendency toward higher TIMI 3 flow rates in comparison with UFH. The rates of other clinical events, such as late infarct-related arterial reocclusion and recurrent ischaemia, were also reduced with LMWH compared with UFH.

**Authors' conclusions**
LMWH could potentially replace UFH as the antithrombotic agent of choice across the spectrum of ACS. In addition, they may potentially be a safe and efficacious antithrombotic agent for PCI. However, further study is warranted to define the benefit of LMWHs in certain high-risk subgroups before their use can be universally recommended.

**CRD commentary**
The review question was broad, but well defined in terms of the intervention, participants and study designs. Only one database was searched for relevant studies and it was not stated whether any language restrictions were applied. Some efforts were, however, made to identify unpublished literature. The review methodology was unclear in terms of how the studies were selected for the review and how the data were extracted. Thus, it is not known whether any formal efforts were made to reduce bias and errors. In addition, since study quality was not formally assessed, it was not
possible to examine how the quality of the included studies might have influenced the results of the review. Data from the studies were tabulated. The authors discussed the results from some of the trials, but not all, in a narrative discussion. Overall, the authors’ conclusions may not be robust.

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

Research: The authors stated that more clinical data on the safety of LMWHs in elderly patients and in combination with platelet inhibitors, such as thienopyridines and glycoprotein IIb/IIIa, are needed before their routine adoption in the setting of STEMI and PCI.

Bibliographic details

PubMedID
12525234

Original Paper URL
http://jama.ama-assn.org/

Other publications of related interest
This additional published commentary may also be of interest. Hillegass WB, Brott BC. Review: low-molecular-weight heparin is effective and safe in the acute coronary syndromes. ACP J Club 2003;139:58.

Indexing Status
Subject indexing assigned by NLM

MeSH
Angina, Unstable /therapy; Angioplasty, Balloon, Coronary; Clinical Trials as Topic; Fibrinolytic Agents /therapeutic use; Heparin /therapeutic use; Heparin, Low-Molecular-Weight /therapeutic use; Humans; Myocardial Infarction /therapy; Platelet Aggregation Inhibitors /therapeutic use; Platelet Glycoprotein GPIIb-IIIa Complex /antagonists & inhibitors; Thrombolytic Therapy

AccessionNumber
12003008300

Date bibliographic record published
31/01/2006

Date abstract record published
31/01/2006

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.