Review: No convincing difference exists between unfractionated and low-molecular-weight heparin in the acute coronary syndrome


QUESTION
In aspirin-treated patients who have the acute coronary syndrome without ST elevation, what are the effectiveness and safety of low-molecular-weight heparin (LMWH) relative to those of unfractionated heparin (UH)?

DATA SOURCES
Studies were identified by searching MEDLINE and EMBASE/Excerpta Medica, searching informally, scanning reference lists, and contacting experts.

STUDY SELECTION
Studies were selected if they were randomized controlled trials (RCTs) that included aspirin-treated patients with unstable angina or non–Q-wave myocardial infarction (MI) who were allocated to UH or LMWH.

DATA EXTRACTION
Data were extracted on patient characteristics, treatment type and duration, and outcome measures.

MAIN RESULTS
12 trials (17 157 patients) met the selection criteria. 5 trials compared LMWH with UH and found that in the short term (7 d), no difference existed between the groups for death or MI at the completion of treatment (Table). 3 trials found that short-term LMWH reduced recurrent angina more than did UH (summary odds ratio [OR] 0.84, 95% CI 0.71 to 1.00, \( P = 0.05 \)). 8 trials compared LMWH or UH with placebo or a control and found that in the short term, LMWH or UH led to fewer deaths or MIs (Table). 5 trials compared LMWH with placebo and found that in the long term (up to 3 mo), no difference existed between the groups for death or MI (Table); however, long-term LMWH led to a higher risk for major bleeding (equivalent to 12 major bleeds/1000 patients treated, summary OR 2.26, CI 1.63 to 3.14).

CONCLUSION
In aspirin-treated patients who have the acute coronary syndrome without ST elevation, no convincing evidence exists to show a difference in effectiveness between unfractionated heparin and low-molecular-weight heparin.

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Comparison of low-molecular weight heparin (LMWH), unfractionated heparin (UH), placebo (P), and a control (C) in the acute coronary syndrome without ST elevation*

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Comparisons</th>
<th>Event rates</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or MI (7 d)</td>
<td>LMWH vs UH</td>
<td>2.2% vs 2.3%</td>
<td>12% (–12 to 31)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Death or MI (7 d)</td>
<td>LMWH or UH vs P or C</td>
<td>4.5% vs 7.4%</td>
<td>45% (26 to 60)</td>
<td>30 (23 to 53)</td>
</tr>
</tbody>
</table>

RRI (CI) | NH (CI)
---|---
Death or MI (up to 3 mo) | LMWH vs P | 4.2% vs 3.9% | 1.9% (–16 to 18) | Not significant |

*MI = myocardial infarction. Other abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.

COMMENTARY
RCTs have convincingly shown the benefit of platelet antagonism with aspirin in the acute coronary syndrome. Inhibiting the coagulation system with heparin (either UH or LMWH), as noted in this analysis, augments the benefit of antithrombotic therapy. The advent of platelet glycoprotein IIb/IIIa antagonists, both in and out of the cardiac catheterization laboratory, also provides incremental benefit beyond “conventional” anticoagulation. How then does the clinician choose the most appropriate treatment option or combination of options?

RCTs are the tried-and-true starting point for evidence-based therapeutics, but they have limitations. The role of a meta-analysis assumes importance when single trials provide conflicting results, exhibit scarce end points, or are characterized by composite outcomes, the components of which may not be equivalent in importance. The meta-analysis by Eikelboom and colleagues provides mixed support for the clinical efficacy of the inhibition of the coagulation system with heparin in patients with the acute coronary syndrome: The results show short-term (7 d) benefits that do not appear to be augmented by continuation of heparin to 3 months.

The comparison of LMWH with UH failed to show a statistically significant effect on the short-term risk for death or MI. Confounding this conclusion, however, is the variable frequency and timing of catheter-based therapy. Such intervention increases myocardial-specific enzymes and affects the frequency of the end point of “MI.” Given the inclusion of > 12 000 patients in this analysis, an underpowered analysis was unlikely. The inclusion of different species of LMWH, all of which have different anti-Xa and anti-IIa activity and bioavailability, further limits this analysis.

Whether LMWH can contribute independently to reduced risk for death or MI in the era of platelet glycoprotein IIb/IIIa antagonists remains to be shown. The powerful effect of the latter on risk for death or MI might overwhelm the ability to detect more modest effects associated with LMWH.

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