Low molecular weight heparin (enoxaparin) in the management of unstable angina: the ESSENCE study

K A A Fox, on behalf of the ESSENCE Study Investigators

The evidence that aspirin improves outcomes in unstable angina is both clear and overwhelming. The same cannot be said for the combination of aspirin and unfractionated heparin (UFH) compared with aspirin alone. All the trials conducted in this area have been underpowered to detect significant difference in the risk of death, myocardial infarction (MI), and recurrent ischaemia. A pooled analysis does suggest that UFH is superior to placebo in the presence of aspirin, but no single trial has been able to confirm this, nor have trials of sufficient size been performed. Treatment with UFH is associated with a significant failure rate, for which a number of explanations have been suggested. Firstly, the anticoagulant effect of UFH is unpredictable and, despite regular monitoring, many patients are not maintained within the optimum activated partial thromboplastin time (aPTT) range of 1.5–2.5 times control. Secondly, UFH is susceptible to binding by plasma proteins and neutralisation by platelet factor IV. Thirdly, a rebound phenomenon has been identified after the cessation of UFH. This has been demonstrated, especially in the absence of aspirin. Fourthly, the antiplatelet effects of aspirin may be overcome in the presence of a potent stimulus from disrupted plaque.

Low molecular weight heparins (LMWHs) have advantages over UFH that may result in greater efficacy and safety, as well as the practical advantages of subcutaneous administration and a predictable anticoagulant effect that removes the need for monitoring. The ESSENCE trial was designed to compare the safety and efficacy of enoxaparin with UFH in patients with unstable angina and non-Q wave myocardial infarction. Enoxaparin is an LMWH with a different chain length and anti-IIa:anti-Xa activity profile compared to other LMWHs.

Methods

The ESSENCE study was a double blind, prospective, randomised trial of 3171 patients recruited from 176 centres in the US, Canada, South America, and Europe. Male and non-pregnant female adults over the age of 18 years were eligible for enrolment. A history of angina at rest lasting for at least 10 minutes during the 24 hours before randomisation was required, as well as evidence of underlying ischaemic heart disease.

<table>
<thead>
<tr>
<th>Time</th>
<th>UFH (n = 1564)</th>
<th>Enoxaparin (n = 1607)</th>
<th>Relative risk reduction (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 hours</td>
<td>115 (7.4)</td>
<td>99 (6.2)</td>
<td>16.2</td>
<td>0.176</td>
</tr>
<tr>
<td>14 days</td>
<td>309 (19.8)</td>
<td>266 (16.6)</td>
<td>16.2</td>
<td>0.019</td>
</tr>
<tr>
<td>30 days</td>
<td>364 (23.3)</td>
<td>318 (19.8)</td>
<td>15.0</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Values are n (%).

Trial acronyms

ESSENCE: Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events
FRAXIS: FRAXiparin in Ischaemic Syndromes
FRIC: FRagmin In unstable Coronary artery disease
FRISC: FRagmin during InStability in Coronary artery disease
GUSTO: Global Use of Strategies To Open occluded coronary arteries
OASIS: Organization to Assess Strategies for Ischaemic Syndromes
PURSUIT: Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy
PARAGON: Platelet IIb/IIIa Antagonists for Reduction of Acute coronary syndrome events in a Global Organization Network
PRISM: Platelet Receptor Inhibition in ischemic Syndrome Management
PRISM PLUS: Platelet Receptor Inhibition in ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms
TIMI: Thrombolysis In Myocardial Infarction
Table 2  Revascularisation rates at 30 days

<table>
<thead>
<tr>
<th>Procedure</th>
<th>UFH (n = 1564)</th>
<th>Enoxaparin (n = 1607)</th>
<th>Relative risk reduction (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>214 (13.7)</td>
<td>198 (12.3)</td>
<td>10.0</td>
<td>0.254</td>
</tr>
<tr>
<td>PTCA</td>
<td>293 (18.7)</td>
<td>236 (14.7)</td>
<td>21.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Total</td>
<td>504 (32.2)</td>
<td>434 (27.0)</td>
<td>16.0</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are n (%).
CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty. Reproduced from Cohen et al with permission of the Massachusetts Medical Society.

Discussion

The ESSENCE study was double blind and prospective. It used a double dummy protocol, whereby all patients received one active treatment and one placebo, to ensure that investigators remained unaware of which treatment their patients received. Blinding remained in place until after the one year follow up survey to eliminate the possibility of investigator bias. Although the duration of treatment was short (range 2–8 days, median 2.6 days), the early benefits of treatment with enoxaparin were fully maintained at one year. The study does not establish whether longer periods of treatment confer additional benefit. These results present a contrast to those of two other major trials of LMWHs, FRIC and FRAXIS.10 11
These two studies used different LMWHs, dalteparin and fraxiparin, and compared them with UFH. In FRIC, there was no significant difference between dalteparin and UFH at any time, although the earlier FRISC trial had shown benefits for dalteparin against placebo. The results of FRIC may have been influenced by sample size and trial design. With only 1400 patients, this study was underpowered and was open during the early period of five to seven days. Other trials such as GUSTO Iib and OASIS have shown that the majority of events occur during this time.

The potential impact of the benefits of enoxaparin need to be seen in the context of other trials in unstable angina and non-Q-wave MI. The benefits achieved are over and above the important impact of aspirin in almost halving the risk of cardiac events. More recently, glycoprotein (GP) IIb/IIIa receptor inhibitors have been introduced and used as adjunctive treatment in patients undergoing PTCA. These agents block the final common pathway of platelet aggregation and potentially offer considerable benefits in unstable angina and non-Q-wave MI. Their largest impact is seen in the highest risk patients and in the context of intervention. Some trials of GP Ib/IIa receptor inhibitors have allowed for the possibility of conservative treatment, with intervention (angiography with or without PTCA; stenting) not forming an obligatory part of the protocol. In the PURSUIT trial, the absolute difference between treatment arms at 30 days for the rate of death or MI was 15 per 1000 patients. An analysis of pooled data from four trials—PURSUIT, PARAGON, PRISM, and PRISM PLUS—shows that the net impact of GP Ib/IIa receptor inhibitor treatment was a reduction in the rate of death or non-fatal MI of 16 patients per 1000 at 30 days. These results appear to be of a similar order of magnitude to the ESSENCE results reported here. It may well be that these two classes of agents—LMWH and GP Ib/IIa receptor inhibitors—could act in a synergistic fashion. Although no trials combining these agents have been performed yet, this will be an intriguing avenue for future research.

Conclusions

Currently, standard treatment for patients presenting with acute coronary syndromes includes a combination of oral aspirin and intravenous UFH, but this regimen fails to prevent further ischaemic events in a substantial number of patients. LMWHs offer a number of advantages over UFH, including reduced binding to plasma proteins, greater resistance to inhibition by platelet factor IV, and a longer plasma half life. These properties result in good bioavailability after subcutaneous administration, with a predictable anticoagulant effect that removes the requirement for aPTT monitoring.

ESSENCE is the first large scale study to show that short term treatment with an LMWH offers long term benefits in acute coronary syndromes, and these findings have practical implications for patient management. For patients with unstable angina or non-Q-wave infarction who are judged to be at high risk of further events, recommended treatment regimens are likely to include subcutaneous LMWH in preference to UFH. Combination with a GP Ib/IIa receptor inhibitor may confer further advantage, but this approach requires testing. More information about the effects of both short and long term enoxaparin treatment will be available when the TIMI 11B study is reported.