A Critical Review of Clinical Trials for Low-Molecular-Weight Heparin Therapy in Unstable Coronary Artery Disease

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Summary:

Unstable angina and non-ST-segment elevation myocardial infarction (MI) are collectively referred to as unstable coronary artery disease (UCAD). They are conditions that share a common pathophysiology and represent frequently encountered, potentially life-threatening clinical manifestations of advanced atherosclerosis. Therefore, treatment of UCAD is a major focus for practicing clinicians, and although pharmacologic agents have been developed that impact on patient outcome, recent data suggest that a further reduction in ischemic complications is possible. Acute-phase treatment with aspirin is associated with a significant reduction in death and nonfatal MI in patients with UCAD. This benefit is enhanced by the addition of unfractionated heparin (UFH) to the treatment strategy; however, UFH requires careful monitoring and titration. In contrast, low-molecular-weight heparins (LMWHs), produced by chemical or enzymatic depolymerization of UFH, yield a predictable and consistent pharmacokinetic profile and anticoagulant response, making them an attractive treatment alternative to UFH in patients with UCAD. The optimal duration of treatment with LMWH is an important question influenced by the observation that reactivation of coagulation occurs following the early and abrupt discontinuation of heparin treatment. Early trials, such as FRISC and FRIC, demonstrated the benefit of acute therapy with dalteparin sodium; however, the results of extended treatment with dalteparin were inconclusive. The extended phase of these studies included relatively low-risk patients, and a once-daily, relatively low-dose strategy was employed. The findings derived from the FRISC II trial, which used a twice-daily dose of dalteparin, suggest a benefit for at least 60 days with extended treatment in high-risk patients with UCAD. Although an early-invasive treatment strategy is particularly beneficial, patients in whom early revascularization is not possible should be considered for extended treatment with dalteparin for up to 45 days, especially those awaiting percutaneous coronary intervention. Extended treatment with dalteparin therefore provides a protective “bridge” to enhance the outcome of patients with UCAD awaiting revascularization.

Key words: low-molecular-weight heparin, unstable angina, non-ST-segment elevation myocardial infarction, antithrombotic therapy

Introduction

Unstable angina and non-ST-segment elevation myocardial infarction (MI) are collectively referred to as unstable coronary artery disease (UCAD). They are conditions that share a common pathophysiology and represent frequently encountered, life-threatening clinical manifestations of advanced atherosclerosis. Estimates suggest that upward of 2.5 million patients worldwide are admitted to hospitals yearly with UCAD. Because the predominant pathophysiologic mechanism involves plaque disruption and platelet-rich thromboembolism, therapy is directed at the thrombotic process.

In the mid 1980s, two multicenter trials demonstrated that aspirin significantly reduced the risk of death or nonfatal MI by 50% in patients with UCAD. Three subsequent, randomized, clinical trials in patients with unstable angina showed that adding 5 to 6 days’ treatment with intravenous unfractionated heparin (UFH) to baseline aspirin therapy produced a trend toward a reduction in the risk of death or nonfatal MI. In a separate study, no difference in efficacy was found between treatment with aspirin alone and treatment with a combination of aspirin and UFH; however, patients received UFH treatment for only 2 days.
Compared with UFH, the more recently developed low-molecular-weight heparins (LMWHs), which are obtained by chemical or enzymatic depolymerization of UFH, exhibit a reduced capacity to catalyze thrombin neutralization (factor IIa) but retain an ability to inactivate factor Xa. They have a longer plasma half-life, a more predictable dose–response relationship with less binding to plasma proteins, endothelial cells, and macrophages, and a more consistent anticoagulation profile than UFH. The predictable anticoagulant response to LMWH makes routine laboratory monitoring of plasma anti-factor Xa unnecessary. Patients with renal insufficiency in whom monitoring is required are an exception to this. Monitoring of plasma anti-factor Xa is difficult and can take several days to obtain reliable results. Another advantage of using LMWH in place of UFH is the lower incidence of heparin-induced thrombocytopenia and less osteoporotic effect with LMWH.9

During the last 15 years, LMWHs have been shown to be at least as effective and safe as UFH for the prevention and treatment of venous thromboembolism. More recently, they have been investigated in the setting of arterial thromboembolism, including UCAD.

One of the practical issues that has arisen with the use of LMWH in place of UFH for patients with UCAD is that discontinuation of treatment prior to catheterization or surgical intervention can be easily overlooked. In this situation, protamine sulphate can be used for urgent reversal of the effect of LMWH: 1 mg protamine sulphate will neutralize 100 IU LMWH. If neutralization is needed within the first 3 h after subcutaneous LMWH administration, 75% of the administered LMWH dose is neutralized with protamine sulphate; 3 to 6 h after LMWH administration, protamine sulphate to neutralize 50% of the LMWH dose is required; and between 6 and 12 h after LMWH administration, protamine sulphate to neutralize 25% of the LMWH dose should be given.

The following review highlights LMWH treatment for UCAD and emphasizes the potential benefit and clinical indication supporting extended therapy in selected patient populations.

Clinical Trials to Determine the Efficacy of Low-Molecular-Weight Heparins

Since the publication of a small trial comparing the efficacy of nadroparin plus aspirin, UFH plus aspirin, and aspirin alone,10 six large-scale, randomized, clinical trials using three different LMWHs have been reported.11-17

Low-Molecular-Weight Heparins versus Placebo

The FRagmin during InStability in Coronary artery disease (FRISC) study was the first and only placebo-controlled, large, randomized, double-blind, clinical trial of an LMWH in UCAD. It included 1,506 patients suffering from unstable angina or non-ST-segment elevation MI and compared dalteparin sodium with placebo.11

The study comprised two phases: (1) An acute phase of hospitalization (5–8 days), during which patients received dalteparin as a fixed dose of 120 IU/kg, subcutaneously, every 12 h, or placebo; and (2) an outpatient phase (39 days), during which the dalteparin group was given 7,500 IU, subcutaneously, once daily.

All patients received 75 mg aspirin daily, after an initial dose of 300 mg.

The primary endpoint was the rate of mortality and MI at the end of acute-phase treatment (Day 6). The secondary endpoints were MI and mortality at Day 40, and a composite endpoint, which included mortality, MI, revascularization, and the need for UFH, on Days 6 and 40.

Dalteparin treatment produced a significant reduction in the primary endpoint on Day 6 (relative risk reduction 63%) and secondary composite endpoint on Days 6 and 40 (relative risk reductions 48 and 21%, respectively) (Table I). At the end of the outpatient treatment period (Day 40), the therapeutic benefit of dalteparin was maintained for the composite endpoint but not for mortality and MI alone.

Dalteparin was well tolerated and treatment compliance was excellent, with only 10% of patients discontinuing treatment during the outpatient phase.

Low-Molecular-Weight Heparins versus Unfractionated Heparin

Since the FRISC trial, no further placebo-controlled studies of LMWHs as acute treatment of UCAD have been carried out. Four comparative trials of intravenous UFH versus subcutaneous LMWH, in addition to aspirin, have been reported.12-15

The primary objective of the FRagmin In unstable Coronary artery disease (FRIC) trial was to investigate the effectiveness of extended anticoagulation with a low dose of dalteparin following acute-phase treatment of UCAD during hospitalization. From Days 6 to 45, patients received either dalteparin or placebo as once-daily subcutaneous injections.

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**Table I** FRISC trial results

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Days</th>
<th>Placebo (%)</th>
<th>Dalteparin (%)</th>
<th>Relative risk reduction (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality + MI</td>
<td>6</td>
<td>4.8</td>
<td>1.8</td>
<td>63</td>
<td>0.001</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality + MI</td>
<td>40</td>
<td>10.7</td>
<td>8</td>
<td>25</td>
<td>0.07</td>
</tr>
<tr>
<td>Mortality + MI + revascularization + UFH</td>
<td>6</td>
<td>10.3</td>
<td>5.4</td>
<td>48</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>25.7</td>
<td>20.5</td>
<td>21</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Abbreviations: MI = myocardial infarction, UFH = unfractionated heparin, revascularization = coronary revascularization.*
acute-phase treatment with dalteparin versus UFH was a secondary aim of the trial.12

The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) trial was designed to determine whether enoxaparin was more effective than UFH in the acute management of patients with UCAD.13

The FRAXiparinx in Ischaemic Syndrome (FRAXIS) trial was designed to compare the effects of two dosing regimens of nadroparin, one administered for 6 ± 2 days, and the other for 14 days, with UFH given for 6 ± 2 days.14

The main objective of the Thrombosis In Myocardial Infarction (TIMI) 11B trial was to test the benefit of a strategy of prolonged anticoagulant therapy with enoxaparin compared with standard treatment with UFH in patients with UCAD.15

The primary endpoints and the treatment regimens of these four trials are reported in Table II. The efficacy endpoints and the rates of major hemorrhage are summarized in Tables III and IV.

Considered collectively, the results demonstrate conclusively that LMWHs combined with aspirin are at least as effective and safe as UFH during acute-phase treatment.

Of the three LMWHs evaluated in clinical trials that have included patients with UCAD, only one—enoxaparin—showed a benefit over UFH. The FRIC and FRAXIS trials demonstrated no difference between dalteparin and nadroparin compared with UFH. There are several possible explanations for the divergent results, as addressed below.

Differences in clinical activity: One possible explanation for the apparent divergent trial outcomes is the intrinsic pharmacologic differences between the LMWHs. In particular, some have argued that the higher anti-Xa:anti-IIa ratio of enoxaparin gives rise to a more potent antithrombotic effect. However, this is an unlikely explanation as enoxaparin and nadroparin are similar regarding anti-Xa:anti-IIa activity (Table V) and yet enoxaparin has been shown to have any benefit over UFH treatment. Also arguing against a role for pharmacologic differences in the divergent results is the fact that nadroparin and enoxaparin have similar mean molecular masses and plasma half-lives (Table V).

Trial objective and design: A second possibility for divergent outcomes relates to major differences in trial objectives, patient selection and population, definition of endpoints, and the dose and duration of UFH treatment. It has already been noted that each clinical study had a different primary objective. The FRIC trial was not powered to detect a difference between dalteparin and UFH. In addition, there were differences in the times at which endpoints were assessed: 6 and 45 days in FRIC, 48 h and 14 days in ESSENCE, 6 and 14 days in FRAXIS, and 14 and 43 days in TIMI 11B.

Patient selection and population profile: The time of enrollment following the onset of chest pain varied in each of the four trials. Patients were recruited for up to 72 h in the FRIC trial, 48 h in the FRAXIS trial, and within 24 h in the two studies with enoxaparin. Therefore, it is likely that the patient populations differed with regard to UCAD severity. Patients evaluated within 24 h of symptom onset represent an inherently sicker and higher-risk group than those seen later on.

In support of this observation, approximately 25% of patients in FRIC and FRAXIS had experienced a prior MI, while these percentages were 46 and 32%, respectively, in the primary endpoints—treatment regimens

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Primary endpoint</th>
<th>Treatment regimen</th>
<th>Treatment regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRIC (1,482)</td>
<td>Death/myocardial infarction/ recurrent angina, Days 6–45</td>
<td>Dalteparin</td>
<td>Unfractionated heparin</td>
</tr>
<tr>
<td>ESSENCE (3,171)</td>
<td>Death/myocardial infarction/ recurrent angina at Day 14</td>
<td>Enoxaparin</td>
<td>Acute phase: IV bolus: 5,000 IU + IV infusion (APTT = 55 to 85 s) 2.6 days (median)</td>
</tr>
<tr>
<td>FRAXIS (3,468)</td>
<td>Death/myocardial infarction/ refractory or recurrent angina at Day 14</td>
<td>Nadroparin</td>
<td>Acute phase: IV bolus: 86 IU/kg + 86 IU/kg/12 h s.c. 6 days or: IV bolus: 86 IU/kg + 86 IU/kg/12 h s.c. 14 days</td>
</tr>
<tr>
<td>TIMI 11 B (4,021)</td>
<td>Death/myocardial infarction/ urgent revascularization at Day 43</td>
<td>Enoxaparin</td>
<td>Acute phase: IV bolus: 70 IU/kg + IV infusion 15 IU/kg/h (APTT adjusted: 1.5–2.5 × control) 3 days Extended treatment: Placebo 43 days</td>
</tr>
</tbody>
</table>

Abbreviations: LMWH = low-molecular-weight heparin, APTT = activated partial thromboplastin time, s. c. = subcutaneous, b.i.d. = twice daily, IV = intravenous.
Moreover, the ESSENCE and TIMI 11B studies had a higher proportion of patients with non-ST-segment elevation MI (21 and 35%, respectively), than FRIC and FRAXIS (16% in each study).

**Definition of endpoints:** A triple composite endpoint was used to assess the efficacy of treatment in each study: death, MI, and recurrent angina or urgent revascularization. Death and MI are considered “hard” endpoints which are not dependent on subjective interpretation, whereas the definition of recurrent angina varies considerably from trial to trial.

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**Table III**  
Low-molecular-weight heparin in unstable coronary artery disease—efficacy results

<table>
<thead>
<tr>
<th></th>
<th>6 Days</th>
<th>14 Days</th>
<th>35–45 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FRIC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dalteparin</td>
<td>9.3%</td>
<td>No data</td>
<td>12.3%</td>
</tr>
<tr>
<td>UFH</td>
<td>7.6%</td>
<td>No data</td>
<td>12.3%</td>
</tr>
<tr>
<td><strong>ESSENCE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>No data</td>
<td>16.6%</td>
<td>No data</td>
</tr>
<tr>
<td>UFH</td>
<td>19.8%</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td><em>p</em></td>
<td></td>
<td>&lt; 0.02</td>
<td></td>
</tr>
<tr>
<td><strong>FRAXIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadroparin 6-day treatment group</td>
<td>13.8%</td>
<td>17.8%</td>
<td>No data</td>
</tr>
<tr>
<td>Nadroparin 14-day treatment group</td>
<td>15.8%</td>
<td>20.0%</td>
<td>No data</td>
</tr>
<tr>
<td>UFH</td>
<td>14.9%</td>
<td>18.1%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>TIMI 11B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>14.2%</td>
<td>17.3%</td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>16.6%</td>
<td>19.6%</td>
<td></td>
</tr>
<tr>
<td><em>p</em></td>
<td></td>
<td>&lt; 0.03</td>
<td>&lt; 0.049</td>
</tr>
</tbody>
</table>

**Abbreviations:** UFH = unfractionated heparin, NS = not significant.

**Table IV**  
Low-molecular-weight heparin in unstable coronary artery disease—safety results: incidence of major bleeding

<table>
<thead>
<tr>
<th></th>
<th>6 Days</th>
<th>14 Days</th>
<th>35–45 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FRIC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dalteparin vs. UFH</td>
<td>1.1 vs. 1% (NS)</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Dalteparin vs. placebo</td>
<td>No data</td>
<td>No data</td>
<td>0.5 vs. 0.4% (NS)</td>
</tr>
<tr>
<td><strong>ESSENCE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin vs. UFH</td>
<td>No data</td>
<td>No data</td>
<td>6.5 vs. 7% (NS)</td>
</tr>
<tr>
<td><strong>FRAXIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadroparin 6-day treatment group vs. UFH</td>
<td>0.7 vs. 1.1% (NS)</td>
<td>1.5 vs. 1.6% (NS)</td>
<td>No data</td>
</tr>
<tr>
<td>Nadroparin 14-day treatment group vs. UFH</td>
<td>1.3 vs. 1.1% (NS)</td>
<td>3.5 * vs. 1.6% (p &lt; 0.02)</td>
<td>No data</td>
</tr>
<tr>
<td><strong>TIMI 11B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin vs. UFH</td>
<td>No data</td>
<td>1.5 vs. 1% (NS)</td>
<td>No data</td>
</tr>
<tr>
<td>Enoxaparin vs. placebo</td>
<td>No data</td>
<td>No data</td>
<td>2.9 vs. 1.5% (p = 0.02)</td>
</tr>
</tbody>
</table>

*Major bleeding in nadroparin 14-day treatment group significantly greater than in nadroparin 6-day treatment group and in UFH group (p<0.02). Abbreviations as in Table III.*

**Table V**  
Pharmacologic properties of different low-molecular-weight heparins (European Pharmacopeia 1997)

<table>
<thead>
<tr>
<th></th>
<th>Anti-factor Xa/IIa ratio</th>
<th>Mean molecular mass (daltons)</th>
<th>Plasma half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>1.9</td>
<td>6000 (5600–6400)</td>
<td>2.8</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>3.3–5.3</td>
<td>4500 (3500–5500)</td>
<td>4.1</td>
</tr>
<tr>
<td>Nadroparin</td>
<td>2.5–4.0</td>
<td>4300 (3600–5000)</td>
<td>3.7</td>
</tr>
</tbody>
</table>
In the ESSENCE and TIMI 11B trials, recurrent angina was defined as angina at rest, of at least 5 min duration, associated with either a new ST-segment shift or T-wave inversion on electrocardiography (ECG); as angina which prompted revascularization; or as postdischarge angina which necessitated rehospitalization. In the FRIC study, recurrent angina was defined as chest pain requiring an intravenous nitroglycerin infusion, and in the FRAXIS trial as recurrent angina associated with ST-segment changes on the ECG with no increase in serum biochemical markers of cardiac injury.

Regimen and duration of unfractionated heparin treatment: In all four comparative studies, LMWHs were administered twice daily as weight-adjusted, subcutaneous injections during the acute phase of treatment. The dosing strategies chosen for LMWH during the acute phase of the FRIC, ESSENCE, and TIMI 11B trials were selected for validated effectiveness and were consistent between studies. Conversely, with UFH, the target therapeutic range for activated partial thromboplastin time (APTT) varied widely among the trials (Table II).

The duration of UFH therapy differed between trials: 5 to 6 days in FRIC and FRAXIS and 2 to 3 days in ESSENCE and TIMI 11B. Under normal circumstances it requires 24 to 48 h to reach a target level of anticoagulation with UFH, whereas an effective level is achieved rapidly with LMWH. In a clinical setting, 2 days’ treatment with UFH and aspirin did not reduce the incidence of MI or death in patients with UCAD compared with those treated with aspirin alone, while a significant benefit was reported with a longer duration of UFH treatment (5–6 days).7

Implications for Acute Phase Treatment

The addition of UFH or LMWH to aspirin for up to 7 days after an episode of UCAD reduces the incidence of death or MI by approximately 50%. A meta-analysis of randomized clinical trials to date, comparing identical durations of treatment with LMWH versus UFH, revealed no clear difference between them in terms of efficacy during acute phase treatment. However, the practical advantages of using LMWH are important factors influencing clinical decisions. It must be considered that a more clinician-friendly treatment strategy will lead to a more widescale and comprehensive management of patients with UCAD.

Duration of Low-Molecular-Weight Heparin Treatment

Extending the duration of antithrombotic treatment has been proposed as a method for achieving stabilization of the unstable coronary plaque, based on the recognition that the risk for recurring events remains high even among patients who achieve early clinical stabilization. The potential benefit of extended antithrombotic therapy has been evaluated in several clinical trials. In the FRIC trial, dalteparin was continued at a dose of 7,500 IU once daily for 39 days without demonstrating additional beneficial effect. The patient population had a relatively low-risk profile, that is, few patients exhibited non-ST-segment elevation MI. In TIMI 11B, no additional benefit was reported with extended treatment with enoxaparin (40 or 60 mg twice daily, for 43 days) but there was a significant increase in major bleeding.

The FRISC trial indicated that extended dalteparin treatment (120 IU/kg every 12 h for 5–8 days, followed by 7,500 IU once daily) might benefit some patients with UCAD. An analysis of several selected patient subgroups within the study showed that the beneficial effect in reduction of death and/or MI seen at Day 6 was maintained at Day 40 in nonsmokers (80% of the study population: relative risk reduction 40%, p = 0.003), those with non-ST-segment elevation MI (38%), and high-risk patients, defined by age > 70 years, diabetes mellitus, previous history of MI, or treatment for heart failure. During extended therapy there was an increasing, significant difference between placebo- and dalteparin-treated patients among those with plasma troponin T levels greater than 0.1 µg/l (patients at high risk for future ischemic events): at Day 40 the relative risk reduction in death and/or MI was 48% with dalteparin treatment (p < 0.01). No protective effect of extended treatment could be demonstrated in patients with very low or undetectable levels of troponin T. These data suggest that early analysis of troponin T might identify high-risk patients with UCAD who are likely to benefit from extended LMWH therapy.

The possibility that risk stratification could guide the selection of the most appropriate management strategy was evaluated in FRISC II (FRagmin and Fast Revascularization during InStability in Coronary artery disease). FRISC II took a different approach to previously conducted studies and examined extended treatment (at an efficacious dose) in high-risk patients. Thus, FRISC II provides valuable information on optimizing dosing regimens to achieve maximum efficacy without compromising safety.

The FRISC II Trial: An Answer to Two Key Questions

**Trial design:** The two important questions to be considered in the management of patients with UCAD are:

1. What is the efficacy and safety of LMWH in the extended treatment of patients with UCAD?
2. What is the value of an early invasive strategy versus a selective noninvasive strategy in addition to an optimum background of antithrombotic medication?

The FRISC II study was a prospective, randomized, parallel-group, multicenter trial. A factorial design was applied to compare invasive versus noninvasive management and extended versus acute-phase dalteparin treatment (Fig. 1). The primary endpoint for the comparison of acute-phase versus extended-term dalteparin treatment was death or MI at 3 months. The corresponding endpoint for the comparison of the early-invasive strategy with the selective noninvasive strategy was death or MI at 6 months. The employment of “hard” endpoints is an attractive feature of this trial.

The FRISC II study population (3,489 patients) included men of at least 40 years of age and postmenopausal women who, within the previous 48 h, had experienced an episode of
chest pain associated with ECG changes or elevated levels of biochemical markers of myocardial ischemia. Patients were eligible for inclusion in the trial if they exhibited symptoms of ischemia that were either increasing, occurring at rest, or giving rise to suspicion of acute MI. Exclusion criteria included an increased risk of bleeding; indication for, or treatment with, fibrinolytics during the prior 24 h; percutaneous transluminal coronary angioplasty (PTCA) within the last 6 months; or a contraindication to early revascularization. Patients with a contraindication to early revascularization were assigned to a noninvasive strategy and randomized to receive dalteparin or placebo during the extended-treatment period.

On admission, all patients received aspirin, beta blockers, calcium antagonists, and nitrate according to clinical guidelines, as well as subcutaneous dalteparin 120 IU/kg/12 h or UFH. At randomization, all patients were changed to the dalteparin regimen. Those in the selective noninvasive strategy continued the dalteparin regimen for 5 to 7 days until an exercise test had been performed. Those in the early intervention arm of the trial received dalteparin for at least 5 days and always until the invasive procedure, which was usually performed within 7 days of admission. Thereafter, the randomized medication was given as twice-daily subcutaneous injections of either dalteparin or placebo. The randomized, twice-daily dose was 5,000 IU in women < 80 kg and men < 70 kg. Heavier patients received 7,500 IU twice daily. This treatment was given by self-injection for an additional 3 months.

Results

Efficacy and Safety of Extended Treatment with Dalteparin

In all, 2,267 subjects were included in the noninvasive arm of the FRISC II trial. The results at 3 months demonstrated a 19% relative and 1.3% absolute reduction in death or MI in the dalteparin group, which was not statistically significant (p = 0.17). However, a clear difference in the incidence of death or MI was observed for at least 45 days during the extended-treatment period. At Day 30, the incidence of death or MI was 3.1% in the dalteparin group compared with 5.9% in the placebo group, a significant relative reduction of 47% (p = 0.002) (Fig. 2A). At 3 months, there was a significant reduction in death, MI, or revascularization of 13% (p = 0.031). The corresponding figure at Day 30 was a 24% reduction in the dalteparin group (p = 0.001)(Fig. 2B). An increased risk of bleeding complications with extended dalteparin treatment compared with acute-phase treatment (2.2 vs. 1.2%) was considered acceptable in view of the clinical benefits.

Invasive versus Noninvasive Treatment

In all, 2,457 patients were randomized to either invasive or noninvasive treatment strategy. Coronary angiography was performed within the first 7 days on 96 and 7% of patients in the invasive and noninvasive groups, respectively, and revascularization was performed within the first 10 days in 71 and 9% of patients, respectively.

After 6 months, there was a decrease in the composite end-point of death or MI of 9.4% in the invasive group compared with 12.1% in the noninvasive group (p = 0.031). There was a significant decrease in MI alone, 7.8 versus 10.1% (p = 0.045), and a nonsignificant reduction in mortality, 1.9 versus 2.9% (p = 0.10). Symptoms of angina and the rate of hospital readmission were halved by the invasive-treatment strategy at 6 months. The findings were independent of the randomized dalteparin treatment and the greatest benefit occurred in high-risk patients. There were slightly more major bleeding episodes in the invasive than in the noninvasive treatment group, but no difference in rates of stroke, intracranial bleeding, or thrombocytopenia. The risk of bleeding associated with revascularization procedures was low with dalteparin treatment.

At 12 months there was a significant risk reduction in death alone (2.2 vs. 3.9%), MI alone (8.6 vs. 11.6%), and the combi-

Fig. 1 FRISC II study design. FRISC II compared the effects of extended treatment with dalteparin versus placebo, and early revascularization versus noninvasive therapy, in patients with unstable coronary artery disease. Patients assigned to the noninvasive group after May 1998 were not included in the secondary analysis and n = 1,235.
nation of death and MI (10.4 vs. 14.2%) in the invasive compared with the noninvasive treatment group.26 In patients who were randomized to early revascularization, no additional beneficial effect of extended dalteparin treatment was seen. For patients in the noninvasive randomized group who had ischemia-driven revascularization within 45 days, the additional beneficial effect of extended dalteparin treatment was highly significant after 1 year, but was not present after 1 year in those patients who did not receive invasive treatment (Wallentin, personal communication).

Discussion

Based on data derived from several large-scale clinical trials, there is general agreement that LMWHs are at least as effective and safe as UFH in the acute treatment of patients with UCAD. The addition of either LMWH or UFH to a background of aspirin reduces the risk of death or MI by approximately 50% in the short term. In view of the practical advantages of LMWH compared with UFH, its use is becoming more widespread in arterial thrombotic disorders. Defining potential differences in efficacy and safety between LMWH preparations awaits the results of head-to-head comparisons in the form of randomized trials.20

The reliable measurement of troponin T and I at the patient’s bedside allows rapid risk assessment and can contribute to management decisions.25, 27, 28 Patients with elevated troponin T levels have been shown to benefit from extended antithrombotic therapy with dalteparin.11, 17

The merits of utilizing an antiplatelet glycoprotein (GP) llb/llla inhibitor to complement antithrombotic therapy in the management of high-risk patients with UCAD have been debated.29 While the combined use of GP llb/llla inhibitors and LMWH may be beneficial for patients undergoing revascularization,30 the Global Utilization of Streptokinase and t-PA for Occluded coronary arteries (GUSTO) IV acute coronary syndrome (ACS) substudy showed no advantage in combining abciximab with dalteparin and aspirin for patients with UCAD not undergoing early revascularization.31 The study demonstrated similar rates of bleeding with GP llb/llla inhibitor in combination with either UFH or dalteparin.

The FRISC II trial is the only large-scale, controlled clinical trial showing a benefit from extended treatment with LMWH in high-risk patients with UCAD. Extended therapy with dalteparin, in addition to aspirin and anti-ischemic medication, significantly reduced the risk of death and MI during the first 45 days and the combined risk of death, MI, and need for revascularization for 90 days.17 Dalteparin is the only LMWH for which the optimal dose and duration of treatment have been identified for an effective and safe treatment of UCAD. Although an early intervention strategy (percutaneous coronary interventions or coronary artery bypass surgery) for revascularization in patients with UCAD is recommended, the early effects of extended dalteparin treatment are useful for protection against further complications while patients are waiting for these invasive procedures. In summary, extended dalteparin treatment for up to 45 days is efficacious and well tolerated, and therefore provides a “bridge” to revascularization when early invasive procedures are not immediately available.

References


\[\text{RR} = \frac{\text{Risk in the invasive group}}{\text{Risk in the noninvasive group}}\]

\[\text{Time since start of double-blind period (days)}\]

\[\text{Probability of death or MI}\]

\[0.00 \quad 0.01 \quad 0.02 \quad 0.03 \quad 0.04 \quad 0.05 \quad 0.06 \quad 0.07 \quad 0.08 \quad 0.09 \quad 0.10\]

\[\text{Time since start of open-label dalteparin (days)}\]

\[0.00 \quad 0.10 \quad 0.20 \quad 0.30 \quad 0.40\]

\[\text{Probability of death or MI, or revascularization}\]

\[0.00 \quad 0.02 \quad 0.04 \quad 0.06 \quad 0.08 \quad 0.10 \quad 0.12 \quad 0.14 \quad 0.16 \quad 0.18 \quad 0.20 \quad 0.22 \quad 0.24 \quad 0.26 \quad 0.28 \quad 0.30 \quad 0.32 \quad 0.34 \quad 0.36 \quad 0.38 \quad 0.40 \]

\[\text{Placebo (n = 1,056) Dalteparin (n = 1,049)}\]

\[\begin{array}{ccccccc}
0.00 & 0.02 & 0.04 & 0.06 & 0.08 & 0.10 & 0.12 \\
0.00 & 0.04 & 0.08 & 0.12 & 0.16 & 0.20 & 0.24 \\
0.00 & 0.04 & 0.08 & 0.12 & 0.16 & 0.20 & 0.24 \\
0.00 & 0.04 & 0.08 & 0.12 & 0.16 & 0.20 & 0.24 \\
\end{array}\]

\[\text{RR (95\% CI) p}\]

\[\begin{array}{ccccccc}
0.81 (0.60–1.10) & 0.017 & 0.76 (0.65–0.89) & 0.001 & 0.77 (0.65–0.91) & 0.021 & 0.76 (0.65–0.89) & 0.001 \\
0.81 (0.61–1.07) & 0.17 & 0.76 (0.65–0.89) & 0.001 & 0.77 (0.65–0.91) & 0.021 & 0.76 (0.65–0.89) & 0.001 \\
0.81 (0.61–1.07) & 0.17 & 0.76 (0.65–0.89) & 0.001 & 0.77 (0.65–0.91) & 0.021 & 0.76 (0.65–0.89) & 0.001 \\
0.81 (0.61–1.07) & 0.17 & 0.76 (0.65–0.89) & 0.001 & 0.77 (0.65–0.91) & 0.021 & 0.76 (0.65–0.89) & 0.001 \\
\end{array}\]

\[\begin{array}{ccccccc}
0.02 & 0.04 & 0.06 & 0.08 & 0.10 & 0.12 & 0.14 \\
0.02 & 0.04 & 0.06 & 0.08 & 0.10 & 0.12 & 0.14 \\
0.02 & 0.04 & 0.06 & 0.08 & 0.10 & 0.12 & 0.14 \\
0.02 & 0.04 & 0.06 & 0.08 & 0.10 & 0.12 & 0.14 \\
\end{array}\]


