Benefits of extended treatment with dalteparin in patients with unstable coronary artery disease eligible for revascularization

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Aims The FRISC II trial demonstrated that, for patients with unstable coronary artery disease, an early invasive strategy following acute treatment with dalteparin and aspirin, was superior to a more conservative approach. We evaluated whether it is beneficial to extend treatment with dalteparin to patients eligible for revascularization but for whom these procedures are performed after the initial hospital stay.

Methods and Results As a subanalysis of FRISC II, the efficacy and clinical safety of extended dalteparin treatment (5000 or 7500 IU . 12 h−1 to day 90) compared with placebo was assessed in 1601 patients randomized to a non-invasive group who underwent revascularization only when necessary because of recurring symptoms, (re)infarction, or severe ischaemia. By day 90, 440 patients had undergone revascularization: 267 of these procedures occurred during the double-blind period. All patients initially received acute treatment (5–7 days from day 1) with dalteparin (120 IU / kg−1 12 h−1). The incidence of death and/or myocardial infarction was monitored until revascularization or day 45 and until revascularization or day 90. There was a significant difference in the estimated probability of death and/or myocardial infarction until revascularization or day 90 in favour of dalteparin (log-rank test, \( P=0.0415 \)) and there was a significant reduction in death and/or myocardial infarction in favour of extended dalteparin treatment at day 45, with a 57% relative risk reduction (\( P=0.0004 \)). At day 90 the relative risk reduction was 29%. The safety profile of extended dalteparin treatment was similar to that of acute usage.

Conclusion Extended dalteparin treatment for up to 45 days is effective and safe as a bridging therapy for patients with unstable coronary artery disease awaiting revascularization.


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Key Words: Unstable coronary artery disease, dalteparin, extended treatment, non-invasive management, invasive management, PTCA, CABG, anticoagulant.

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Introduction

In unstable coronary artery disease thrombi at the coronary lesion and raised coagulation activity persist for months after an episode of coronary instability[1,2]. Patients remain clinically vulnerable, even after chest pain has disappeared. The risk of progression to myocardial infarction and death is up to 20% during the first month after an episode of unstable coronary artery disease. Increased risk persists for 3–6 months, despite initial medical stabilization[3]. The Fragmin during instability in coronary artery disease (FRISC) trial showed that the risk of progression to myocardial infarction and death is reduced when patients receive antithrombotic treatment with dalteparin and aspirin[4,5]. The incidence of death and/or
myocardial infarction was 1.8% in patients with unstable coronary artery disease, treated for the first 6 days with dalteparin compared with 4.8% in patients receiving placebo \((P=0.001)\)\(^5\). Consequently, dalteparin, at a dose of 120 IU kg\(^{-1}\) day\(^{-1}\) for 5–7 days, is currently recommended for the acute treatment of unstable coronary artery disease. The Fragmin in unstable coronary artery disease (FRIC) trial showed that dalteparin is as effective and safe as unfractionated heparin in the acute phase\(^6\). However, the benefits of heparins, either unfractionated heparin or low-molecular-weight heparin administered as an acute treatment appear to be short-lived, with reactivation of the disease process within a few hours or days of discontinuing treatment\(^7,8\). This was demonstrated in the FRISC and FRIC studies, which showed a 'rebound' in frequency of death and/or myocardial infarction when dalteparin treatment was discontinued or the dose reduced\(^5,6\).

The Fragmin and fast revascularization during instability in coronary artery disease (FRISC II) trial was designed to resolve two key issues concerning the management of patients with unstable coronary artery disease. The first issue was whether extended treatment with dalteparin (5000 or 7500 IU day\(^{-1}\)) beyond the acute period and until day 90, was beneficial in reducing the incidence of death and acute myocardial infarction\(^9\). The second issue was whether early invasive intervention strategy was superior to a non-invasive, stepwise, selective strategy\(^10\). The study demonstrated that an early invasive approach, in conjunction with aggressive medical treatment (including dalteparin and aspirin) for 5–7 days and always until revascularization, is superior to more conservative strategies\(^10,11\). Unfractionated heparin or low-molecular-weight heparin are generally administered for 5–7 days after presentation of unstable coronary artery disease\(^12\), but there is often a delay between diagnosis and the performance of interventional procedures. For various reasons (e.g. socio-economic), there are wide geographical variations in the timing and capacity of revascularization procedures\(^13–15\). It is therefore important to establish the optimum management of these patients awaiting revascularization procedures.

In the present study, which is a subanalysis of the FRISC II trial data, we set out to evaluate whether it is beneficial to extend treatment with dalteparin in patients eligible for revascularization but for whom procedures are delayed and performed after the acute initial hospital stay.

**Methods**

**Patients**

Men or women with symptoms of angina or suspected myocardial infarction without ST-elevation within 48 h of admission to hospital were eligible for inclusion in the FRISC II study. Myocardial ischaemia was confirmed by electrocardiography (ST-depression ≥0.1 mV or T-wave inversion ≥0.1 mV) or by raised biochemical markers (creatinine kinase-MB >6 µg.l\(^{-1}\), troponin-T >0.10 µg.l\(^{-1}\), positive qualitative troponin-T test, or catalytic activity of creatine kinase, creatine kinase-B, or creatine kinase-MB higher than the diagnostic limit for myocardial infarction). Exclusion criteria were increased risk of bleeding, indication for thrombolysis due to myocardial infarction, recent angioplasty, known sensitivity to heparins, significant structural cardiac disease, or severe underlying systemic disorders.

**Main FRISC II study design**

The FRISC II study was a prospective, randomized, double-blind, placebo-controlled, parallel group trial.
A total of 3489 patients were enrolled from 58 centres in the Scandinavian countries. All patients received open-label dalteparin, 120 IU . kg$^{-1}$ 12 h$^{-1}$, subcutaneously, and aspirin, for the first 5–7 days (acute period). The first day of this treatment was taken as day 1. Randomization to the different treatment regimens took place within 72 h of hospital admission. Patients suitable for invasive revascularization procedures were randomized to either an invasive or a non-invasive group. Patients not suitable for randomization to invasive procedures were assigned to the so-called contraindicated group and handled according to a non-invasive strategy. All patients were simultaneously randomized to either placebo or to dalteparin treatment for the double-blind period, which lasted from the end of the acute period until day 90.

During the double-blind period, patients received twice daily, subcutaneous injections of either dalteparin (5000 IU for women weighing less than 80 kg and men weighing less than 70 kg; 7500 IU for all other patients) or placebo.

**FRISC II subanalysis**

The present study concentrates on the outcome of patients in the non-invasive group only, i.e. those suitable for invasive revascularization who were randomized to the non-invasive group. It excludes the contraindicated group and the invasive group of patients. Patients in the non-invasive group (NI; n = 1601) were treated with a non-invasive, stepwise, selective strategy. Invasive procedures (coronary angiography and revascularization, either PTCA or CABG) were only performed when recurring or incapacitating symptoms, (re)infarction or severe ischaemia upon exercise testing necessitated intervention. In cases of revascularization, patients were taken off the blinded study drug the evening before the procedure and received open-label heparin for the period around the procedure: the last injection of dalteparin was given no later than 12 h before revascularization. Patients who were randomized to the non-invasive group correspond to those patients in usual clinical practice who are eligible for early revascularization but who, according to the protocol, are handled with a non-invasive, stepwise strategy, with revascularization in the event of recurrent angina. The incidence of death or myocardial infarction was monitored from the start of the double-blind period up to revascularization or day 90 (events after revascularization or day 90 were not included).

**End-points**

The primary objective of this subanalysis of the FRISC II trial was to compare the incidence of death and/or myocardial infarction until revascularization or day 90 in patients treated with dalteparin or placebo in the non-invasive group. The incidence of death and/or myocardial infarction was also recorded until revascularization or day 45.

Myocardial infarction was defined by the occurrence of two of the three conventional criteria: typical chest pain; diagnostic electrocardiography recording (mainly new Q-wave); or a rise in biochemical markers indicating myocardial damage, as previously outlined\(^9\). Causes of death were established at necropsy. End-point events reported by the core laboratory were adjudicated by an independent clinical-event committee.

Adverse events during the double-blind period to day 90 were documented. The main safety variables were major bleeding (a decrease in haemoglobin level of 20 g . l$^{-1}$ or more with clinical symptoms, a decrease of haemoglobin level of 40 g . l$^{-1}$ or more despite clinical symptoms, bleeding requiring transfusion, intracranial bleeding, or bleeding leading to death) minor bleeding, thrombocytopenia, allergic reaction, and other adverse events. Haematoma at the injection site was only reported if it troubled the patient or required medical intervention.

The study complied with the Declaration of Helsinki, and all local ethics committees approved the protocol.

**Statistical analyses**

The primary analysis used in the main FRISC II study was modified to assess data from patients treated according to the non-invasive strategy who were eligible for randomization to early intervention (the non-invasive group). Dalteparin and placebo treatments were compared regarding the incidence of death and/or myocardial infarction from the start of the double-blind period until revascularization or day 90 on an intention-to-treat basis (log-rank test). Thus events which occurred during the acute treatment period were not included. Patients were excluded from the analysis at the time of revascularization, thus patients already revascularized in the acute treatment period were not included in this comparison.

**Results**

**Patient details**

From 1601 patients entering the study in the non-invasive group, 798 were randomized to receive extended dalteparin during the double-blind period, and 803 to receive placebo. Some patients were withdrawn during the acute treatment phase, before the first double-blind injection (48 randomized to dalteparin and 32 randomized to placebo), and seven died (three randomized to dalteparin and four randomized to placebo). Thus, 747 patients received extended dalteparin treatment and 767 received placebo. The baseline characteristics of these patients were comparable\(^10\).
Efficacy of extended dalteparin treatment

There was a statistically significant reduction in death and/or myocardial infarction in favour of extended dalteparin treatment compared with placebo at day 40 in the double blind period (equals approximately day 45 from the start of the study) (dalteparin 3·6% vs placebo 8·3%, 57% relative risk reduction; \( P = 0·0004 \)). At day 85 in the double-blind period (equals approximately day 90 from start of the study) the relative risk reduction was 29% (dalteparin 6·7%, placebo 9·4%).

There was a statistically significant difference in the estimated probability of death and/or myocardial infarction in favour of dalteparin until revascularization or day 90 (log-rank test, \( P = 0·0415 \)). Investigation of the treatment effect over time shows that dalteparin has a significant benefit vs placebo during the whole period of treatment, but that the difference starts to diminish after about 55 days on double-blind treatment (Fig. 2).

Timing of revascularization in the non-invasive group

In the non-invasive group, approximately 30% of patients underwent revascularization procedures up until day 90. Of these, 80% were performed by day 45 (i.e. within approximately 40 days from the start of double-blind treatment). Revascularization was more frequent in placebo-treated patients and tended to occur earlier in the treatment period than in dalteparin-treated patients (Table 1).

Adverse events

The most frequent adverse event in dalteparin-treated patients was bleeding. Although more bleeding events were reported in the dalteparin group than in the placebo group, this difference was due mainly to a difference in minor bleeding events, such as subcutaneous haematomas. The incidence of bleeding events and stroke in the non-invasive group, during the double-blind period of the study, is given in Table 2. The incidence of major bleeding events was 3·1% in the dalteparin group and 1·8% in the placebo group until day 90 (Table 2). The overall frequency of all types of strokes was low and rates were comparable between the dalteparin and placebo groups (Table 2). A higher rate of haemorrhagic strokes in the dalteparin group was outweighed by a higher rate of ischaemic strokes, in the placebo group. Allergic reactions and other adverse events were not treatment-related. There were no anaphylactic reactions reported or incidences of thrombocytopenia verified as heparin-induced thrombocytopenia in the extended dalteparin treatment period.

The treatment period during which adverse events occurred in dalteparin- and placebo-treated patients is shown in Table 3. No apparent clustering of events was observed at any individual time. In the dalteparin-treated patients, one haemorrhagic stroke was reported from the start of the double-blind period to day 15, there were no haemorrhagic strokes between days 16 and 45 and two were reported between days 46 and 90. Up to 45 days, the risk of bleeding and haemorrhagic stroke is outweighed by the reduction in death and myocardial infarction.

Discussion

This subanalysis of the FRISC II trial demonstrates the marked benefit of extended dalteparin treatment for patients with unstable coronary artery disease who are eligible for revascularization but for whom the
procedure is performed after the initial acute hospital period. There is a significant reduction in death and/or myocardial infarction in patients receiving dalteparin rather than placebo until revascularization or day 45. At day 45, the significant relative risk reduction in death and/or myocardial infarction with extended dalteparin treatment is 57% compared with placebo ($P=0.0004$). The benefit conferred by dalteparin treatment is greatest up to days 45–60 from the start of treatment, after which the difference between treatment groups is less marked.

Revascularization was more frequent in placebo-treated patients and tended to occur earlier in the treatment period than in dalteparin-treated patients. This suggests that dalteparin may stabilize the patient and delay the onset of symptoms requiring urgent invasive therapy.

In contrast to two previous studies with nadroparin and enoxaparin, FRISC II with a fixed twice daily dosing demonstrates that dalteparin provides enhanced protection through extended treatment until revascularization in unstable coronary artery disease$^{[16,17]}$. Based on the evidence derived from the FRISC II trial,

### Table 1  Timing of revascularization in the non-invasive (NI) group

<table>
<thead>
<tr>
<th>Timing of PTCA and/or CABG</th>
<th>Dalteparin (n=747)</th>
<th>Placebo (n=767)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n*</td>
<td>%</td>
</tr>
<tr>
<td>Before double-blind period**</td>
<td>75</td>
<td>10.0</td>
</tr>
<tr>
<td>After 10 days of double-blind treatment</td>
<td>33</td>
<td>4.4</td>
</tr>
<tr>
<td>After 25 days of double-blind treatment</td>
<td>64</td>
<td>8.6</td>
</tr>
<tr>
<td>Increment days 10-25</td>
<td>31</td>
<td>4.2</td>
</tr>
<tr>
<td>After 40 days of double-blind treatment</td>
<td>77</td>
<td>10.3</td>
</tr>
<tr>
<td>Increment days 25-40</td>
<td>13</td>
<td>1.7</td>
</tr>
<tr>
<td>After 55 days of double-blind treatment</td>
<td>87</td>
<td>11.6</td>
</tr>
<tr>
<td>Increment days 40-55</td>
<td>10</td>
<td>1.3</td>
</tr>
<tr>
<td>After 70 days of double-blind treatment</td>
<td>100</td>
<td>13.4</td>
</tr>
<tr>
<td>Increment days 55-70</td>
<td>13</td>
<td>1.8</td>
</tr>
<tr>
<td>After 85 days of double-blind treatment</td>
<td>122</td>
<td>16.3</td>
</tr>
<tr>
<td>Increment days 70-85</td>
<td>22</td>
<td>2.9</td>
</tr>
</tbody>
</table>

*Number of revascularizations.

**All patients treated with dalteparin 120 IU·kg$^{-1}$·12 h$^{-1}$.

Note: 10 days of double-blind treatment is approximately equal to 15 days from the start of the study (day 15).

### Table 2  Incidence of bleeding events and stroke in the double-blind period to day 90

<table>
<thead>
<tr>
<th>Safety variable</th>
<th>Dalteparin (n=747)</th>
<th>Placebo (n=767)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR n (%)</td>
<td>NR n (%)</td>
<td></td>
</tr>
<tr>
<td>Major bleed</td>
<td>740 (3.1)</td>
<td>762 (1.8)</td>
</tr>
<tr>
<td>Minor bleed</td>
<td>739 (22.2)</td>
<td>762 (7.5)</td>
</tr>
<tr>
<td>Stroke</td>
<td>740 (1.1)</td>
<td>762 (0.7)</td>
</tr>
</tbody>
</table>

NR=number of patients reporting.

One event can be presented under more than one heading.

### Table 3  Distribution of adverse events (AE) in the non-invasive (NI) group by time

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Number of patients (%) per treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>From start of double-blind period until day 15</td>
</tr>
<tr>
<td>Non-invasive–dalteparin</td>
<td>n=710</td>
</tr>
<tr>
<td>Patients reporting</td>
<td>702</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>Patients reporting</td>
<td>702</td>
</tr>
<tr>
<td>AE with outcome death</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Non-invasive–placebo</td>
<td>n=708</td>
</tr>
<tr>
<td>Patients reporting</td>
<td>705</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>6 (0.9)</td>
</tr>
<tr>
<td>Patients reporting</td>
<td>706</td>
</tr>
<tr>
<td>AE with outcome death</td>
<td>2 (0.3)</td>
</tr>
</tbody>
</table>

The table only includes events reported up to day 90.

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dalteparin is the only low-molecular-weight heparin for which an optimal dose and duration of outpatient treatment have been established as an effective and safe therapy for patients with unstable coronary artery disease[9].

In the present study, the reduction in dalteparin dose from 120 IU kg⁻¹ 12 h⁻¹ to the extended gender- and weight-adjusted fixed-dose regimen of 5000 IU or 7500 IU 12 h⁻¹ from days 5–7 up to day 90, has no obvious impact on the incidence of death and/or myocardial infarction. Thus, there was no evidence for a rebound effect with a fixed dose of 5000 or 7500 IU twice daily, unlike the effect noted when the dalteparin dose was reduced to the lower dose of 7500 IU once daily, as in the FRISC and FRIC trials[5,6].

The safety profile of extended dalteparin use appears similar to that of the acute usage currently approved. Whilst more bleeding events are reported with dalteparin compared with placebo, they are mainly minor bleeding events, such as subcutaneous haematoma. Up to 45 days, the risks of major bleeding are more than compensated by the significant reduction in death and/or myocardial infarction with dalteparin treatment. Examination of the treatment period during which adverse events occurred shows no clustering of events at any individual time. This indicates that the occurrence of these adverse events is not related to the length of exposure to dalteparin. However it should be noted that the study was not dimensioned to evaluate major bleeding outcome. Patients requiring revascularization were taken off dalteparin treatment the evening before the procedure and no peri-procedural increase in risk of bleeding was registered[18]. The use of low-molecular-weight heparin until revascularization was not a predefined end-point in the FRISC II study. However, given that there can be a number of medical and logistical factors resulting in delays in revascularization procedures, the data suggest that continuing dalteparin until revascularization in this setting has a favourable risk/benefit ratio.

In conclusion, patients with unstable coronary artery disease who are eligible for invasive procedures but for whom the procedure takes place after the initial 5–7 days hospital stay, benefit significantly from extended dalteparin treatment. The FRISC II trial shows that there is a statistically significant difference in the estimated probability of death and/or myocardial infarction (log-rank test, \( P=0.0415 \)) in favour of dalteparin from the start of the double-blind period until revascularization or day 90. A significant 57% relative risk reduction in death and/or myocardial infarction is seen at day 45 (dalteparin 3.6% vs placebo 8.3%, \( P=0.0004 \)). Up to 45 days, the risks of bleeding and haemorrhagic stroke as a result of extended treatment with a fixed dose of dalteparin are clearly outweighed by the significant reduction in death and myocardial infarction.

To summarize, FRISC II demonstrates that dalteparin in a fixed twice daily dosing has a good safety profile and is effective as a bridging therapy for up to 45 days for patients awaiting revascularization.

References