Recurrent Cardiac Ischemic Events Early After Discontinuation of Short-Term Heparin Treatment in Acute Coronary Syndromes

Results From the Thrombolysis In Myocardial Infarction (TIMI) 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) Studies

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OBJECTIVES
The aim of this study was to determine whether discontinuation of low-molecular-weight heparin (LMWH) treatment results in a clustering of cardiac ischemic events as previously observed after cessation of unfractionated heparin (UFH) in acute coronary syndrome (ACS) patients.

BACKGROUND
Clinical trials in patients with ACS have shown early recurrent ischemic events after discontinuation of UFH treatment. We analyzed whether LMWH cessation also results in early ischemic recurrence events and if continuation of a fixed-dose LMWH prevents this complication.

METHODS
The combined incidence of death, myocardial infarction, or urgent revascularization in the first seven days after discontinuation of UFH (n = 3,012), short-term enoxaparin 1 mg/kg subcutaneously twice a day (n = 2,011), and short-term enoxaparin followed by prolonged enoxaparin 60 mg subcutaneously twice a day (n = 1,075) was analyzed from the combined Thrombolysis In Myocardial Infarction (TIMI) 11B/Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) database in a per patient analysis.

RESULTS
The cessation of both UFH and short-term enoxaparin resulted in a similar clustering of recurrent ischemic events on the first day, with an incidence of the primary end point of 2.8% in both groups. Of all recurrent events in the first week after cessation, 40% occurred in the first 24 h. The continuation of a fixed-dose enoxaparin treatment prevented this early excess, with a first day incidence of 0.4% (p ≤ 0.0001). The TIMI risk score characteristics predicted the incidence of early rebound ischemic events.

CONCLUSIONS
There is significant clustering of recurrent ischemic events within 24 h after cessation of both short-term UFH and enoxaparin treatment, and patients should be carefully monitored during that period. This early rebound may be prevented by continuation of a fixed dose of enoxaparin. (J Am Coll Cardiol 2003;42:2083–9) © 2003 by the American College of Cardiology Foundation

Several studies in patients with acute coronary syndromes (ACS) have described the recurrence of ischemic events shortly after cessation of unfractionated heparin (UFH) treatment (1–4). In the Global Use of Strategies To Open occluded arteries in acute coronary syndromes (GUSTO I) study, 33% of all recurrent myocardial infarctions (MIs) occurring in the first week after UFH was discontinued occurred within 10 h (2). In an Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) substudy, a higher incidence of ischemic ST-segment episodes was observed in the 48 h after UFH and low-molecular-weight heparin (LMWH) treatment than during the first 48 h of treatment (3), although the data suggest that the incidence was lower after LMWH treatment than after UFH treatment. A more recent publication also observed this very early clustering of rebound ischemia after discontinuation of UFH, with a peak incidence as early as 4 h after discontinuation (4).

To date, one study (5) reported an increased event rate when therapeutic LMWH treatment was discontinued, reducing its benefit compared with placebo in the acute phase.

We investigated whether cessation of UFH or LMWH resulted in a clinical rebound and whether these compounds differ in this respect. We used data derived from the large ESSENCE (6) and Thrombolysis In Myocardial Infarction...
study the effect of this regimen on rebound phenomena. LMWH treatment arm of the TIMI 11B trial allowed us to ESSENCE studies.

Protocol and patient population of the TIMI 11B and double dummy design, to intravenous UFH (n within 24 h after onset of symptoms, were eligible for prescribed in previous publications (6,7). In short, patients with enoxaparin treatment only (ShortEnox group, n = 3,012), patients who had received short-term in-hospital enoxaparin treatment (ShortEnox group, n = 2,011), and patients who had received short-term in-hospital enoxaparin followed by long-term out-of-hospital continuation of enoxaparin treatment (LongEnox group, n = 1,075).

The time of discontinuation of study drug for patients

Patient selection for the current analysis. All patients from the TIMI 11B and ESSENCE trials were eligible for the present study if they had received in-hospital study treatment (n = 7,081).

Not included were patients in whom study drug treatment times were not available (n = 41), or in whom in-hospital study drug was administered for more than 14 days (n = 5), on oral anticoagulant treatment after study drug treatment (n = 29), or who died during study in-hospital drug treatment (n = 16). We excluded patients who underwent revascularization during study drug treatment because of confounding effects of procedural complications and the use of additional antithrombotic medication (n = 239), and patients who underwent revascularization within 48 h after cessation of study drug without recurrent angina between cessation and revascularization because of the probability that the indication for the intervention was established before study drug discontinuation or irrespective of the clinical course (n = 653). As a result, 6,098 patients were included in the present analysis (Table 1).

We considered the following patient groups: patients who had received short-term UFH (UFH group, n = 3,012), patients who had received short-term in-hospital enoxaparin treatment only (ShortEnox group, n = 2,011), and patients who had received short-term in-hospital enoxaparin followed by long-term out-of-hospital continuation of enoxaparin treatment (LongEnox group, n = 1,075).

The time of discontinuation of study drug for patients

<table>
<thead>
<tr>
<th>Table 1. Patient Selection for Current Analysis</th>
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</thead>
<tbody>
<tr>
<td><strong>Treatment Group</strong></td>
</tr>
<tr>
<td>Randomized</td>
</tr>
<tr>
<td>N = 3,521</td>
</tr>
<tr>
<td>Exclusion</td>
</tr>
<tr>
<td>Treatment &gt;14 days</td>
</tr>
<tr>
<td>Treatment duration missing</td>
</tr>
<tr>
<td>Revascularization during Rx</td>
</tr>
<tr>
<td>Revascularization &lt;48 h after Rx without angina</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
</tr>
<tr>
<td>Death during Rx</td>
</tr>
<tr>
<td>Total exclusion</td>
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<tr>
<td>Total inclusion</td>
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</tbody>
</table>

LongEnox = long-term enoxaparin; Rx = treatment; ShortEnox = short-term enoxaparin; UFH = unfractionated heparin.
treated with UFH was defined as the time at which the infusion was stopped. For patients treated with enoxaparin, the time of discontinuation of treatment was defined as 12 h after the last full in-hospital enoxaparin dose, after which plasma drug levels fall below the therapeutic range.

**End point definitions and data analysis.** The primary end point for the current analysis was a composite of mortality, (recurrent) MI, or recurrent ischemia leading to urgent revascularization occurring after discontinuation. Secondary end points were: mortality; mortality or (recurrent) MI; and mortality, (recurrent) MI, or severe recurrent ischemia with or without urgent revascularization. End point definitions have been presented in the original reports (6,7). A (recurrent) MI was defined as rise of creatine kinase-MB fraction above normal or 50% increase, or creatine kinase rise >2 times upper limit and increased by >25% over previous value, or new Q waves.

The incidence of the primary and secondary end points was calculated for the first 7 days after treatment discontinuation by calculating, for each 24-h period, the percentage of patients who developed a first end point among those patients who had not previously developed that end point. We compared the incidence of the primary end point on the first day after discontinuation with the incidence on the subsequent days. Furthermore, to observe if reactivation of an ischemic event occurred in these stabilized patients (n = 6,098) (Table 1), the incidence of the primary end point of the day before study drug continuation was calculated. By definition, patients who either died or underwent an urgent revascularization during treatment were excluded, thus the incidence of MI was calculated. It is not possible to compare the incidence of clinical events after discontinuation with the incidence during study drug administration, because in the design of this analysis as well as previous similar analyses (4,9), the end points death and revascularization could not occur before discontinuation.

**TIMI risk factors and recurrent ischemic events.** To identify whether cardiac risk factors, identified at randomization, were associated with early rebound events after treatment cessation, the TIMI risk score was related to the incidence of early rebound (10).

**Statistics.** Baseline characteristics between the three groups were compared with an analysis of variance for continuous baseline variables, a chi-square test used for non-continuous variables, and a Kruskal-Wallis analysis for non-parametric variables. Differences between the treatment groups in incidences of the primary and secondary end points were analyzed using the chi-square test. For the relationship between the number of risk factors and the incidence of rebound events, a Wilcoxon test was performed.

**RESULTS**

**Patient characteristics.** The patient characteristics of the UFH group, the ShortEnox group, and the LongEnox group are presented in Table 2. Compared with the UFH and ShortEnox groups, patients in the LongEnox group consisted of more males (±4%), had a lower prevalence of a family history of coronary artery disease (±5%), hypertension (±4%), hypercholesterolemia (±5%), previous MI (±8%), a higher prevalence of aspirin use (±8%), and had a higher number of TIMI risk factors. The in-hospital treatment duration was longer in the LongEnox group.

**Clinical events after study drug discontinuation.** The cumulative incidence of the primary end point during the first seven days after treatment cessation is shown in Figure 1. The UFH and ShortEnox groups showed a significantly
higher incidence of ischemic events compared with the LongEnox group (UFH vs. LongEnox, p < 0.0001; ShortEnox vs. LongEnox, p = 0.0003 at day 7). The greatest difference in event rates was observed on the first day after cessation of treatment.

For the UFH and ShortEnox groups, the incidence of the primary end point on the first day after study drug discontinuation was 2.9% and 2.8%, respectively, and the hazard on day 1 was substantially greater than on subsequent days (i.e., 2 to 7 days) and before discontinuation (i.e., day -1) (Fig. 2, Table 3). In the UFH and ShortEnox groups, 39% and 46%, respectively of all primary end point events in the first week occurred on the first day. The incidence on day 1 and day 2 after cessation in the UFH group was 2.9% and 1.1%, respectively (p < 0.0001), and 2.8% and 0.4% in the ShortEnox group, respectively (p < 0.0001). This early rebound in the UFH and ShortEnox groups was also observed for the separate end points death and MI (Table 3).

An excess of risk during the first 24 h was not observed in the LongEnox group, with constant event rates from day -1 to day 7, with an incidence of the primary outcome on days 1 and 2 after cessation of 0.4% and 0.7%, respectively (p = 0.4).

Reactivation in the patients treated in the UFH and ShortEnox groups was apparent, with event rates on the day before discontinuation of 0.6% in the UFH group and 0.8% in the ShortEnox group, respectively (Table 3). The LongEnox group showed no reactivation with similar event rates on the day before discontinuation and day 1 after cessation (0.2% vs. 0.4%, respectively).

The mean time to the occurrence of clinical events was 7.3 and 9.0 h after the presumed loss of therapeutic UFH and short-term enoxaparin plasma drug levels, respectively (i.e., 7.3 h after discontinuation of UFH infusion, 21 h after last enoxaparin injection). On the first day as well as in the first week, the incidences of the primary end point and of the individual clinical end points were significantly lower in the LongEnox group than in the other two groups (Table 3). Additionally, the combined end points death/MI and death/MI/severe recurrent ischemia showed similar high incidences on day 1 after cessation compared with the following days for both the UFH and ShortEnox groups and not for the LongEnox group (data not shown). The cessation of long-term enoxaparin after six weeks showed no rebound of ischemic events.

TIMI risk factors and recurrent ischemic events. Figure 3 relates the number of TIMI risk factors with the incidence of early rebound (i.e., events within 24 h after the cessation of treatment). In both the UFH and ShortEnox groups, a clear relationship between TIMI risk score and event rate was observed, with an increase in the incidence of early
rebound proportional to the number of risk factors. Patients with TIMI risk scores of 0 to 4 had a rebound incidence of 2.2%, whereas patients with scores of 5 to 7 had an incidence of 4.5%. The LongEnox group revealed no rebound events in the 0/1 and 2 risk-factors groups, and low incidences in the 3, 4, and 5 risk-factors groups of 0.3%, 0.4%, and 1.2%, respectively. No events occurred in patients with 6/7 risk factors; however, there was a very low number of patients in this group (n = 133). At any level of risk, the LongEnox group had a lower incidence of events, with a statistically significant difference in the groups with 2, 3, and 4 risk factors (p = 0.007, p = 0.009, and p = 0.048, respectively, UFH group + ShortEnox vs. LongEnox).

**DISCUSSION**

The discontinuation of both short-term UFH and short-term enoxaparin treatment resulted in a clustering of ischemic events on the first day after cessation of treatment. Of all recurrent end points occurring in the week after discontinuation of these treatments, approximately 40% occurred within 24 h after cessation. Early rebound was observed for death, MI, urgent revascularization, and severe recurrent ischemia, indicating that the composite end point was not driven by a single event.

Moreover, this reactivation of ischemic event occurs in patients who are considered stable, and who may be transferred home or to other facilities on that first day after discontinuation of anticoagulation.

The continuation of a fixed reduced dose of enoxaparin treatment was associated with less early rebound, and with a significantly lower total incidence of recurrent ischemia during one week of follow-up. It was associated with a lower incidence in patients at all levels of risk but was most effective in patients with a TIMI risk score of 3 to 7, where it reduced the primary end point by approximately 80% (Fig. 3). The cessation of long-term enoxaparin treatment did not lead to an increase of events and showed similar incidence rates on days 1 and 2 after cessation.

The TIMI risk scores were different among the three treatments groups (Table 2). However, as the mean risk score in the LongEnox group was higher than in the other two groups, these differences do not explain the lower incidence of rebound in the LongEnox group.

In our analysis, we found no difference in the incidence of rebound events between UFH and short-term enoxaparin (both ±2.8%). In an ESSENCE substudy (3), a higher incidence of ST-segment shifts was observed after UFH treatment compared with that after enoxaparin treatment. However, this was a small study, and (silent) ST-segment shifts may only partially reflect recurrent thrombotic events. Other factors such as tachycardia, anemia, or coronary spasm may contribute to these episodes.

Patients continuing to chronic-phase LMWH treatment

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**Table 3.** Incidence of Ischemic Events on the Day Before Treatment Discontinuation (Day −1), and the First Day and the First Week After UFH or Short-Term Enoxaparin Treatment Cessation

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>UFH (n = 3,012)</th>
<th>ShortEnox (n = 2,011)</th>
<th>LongEnox (n = 1,075)</th>
<th>p Value*</th>
<th>Risk Ratio [95% CI]*</th>
</tr>
</thead>
<tbody>
<tr>
<td>On treatment day −1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>0.6% (19)</td>
<td>0.8% (6)</td>
<td>0.2% (2)</td>
<td>0.2</td>
<td>0.37 [0.09–1.49]</td>
</tr>
<tr>
<td>Off treatment day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>2.9% (86)</td>
<td>2.8% (57)</td>
<td>0.4% (4)</td>
<td>0.000005</td>
<td>0.13 [0.06–0.30]</td>
</tr>
<tr>
<td>Death</td>
<td>0.9% (26)</td>
<td>0.8% (17)</td>
<td>0.1% (1)</td>
<td>0.007</td>
<td>0.16 [0.02–0.55]</td>
</tr>
<tr>
<td>MI</td>
<td>0.6% (17)</td>
<td>0.4% (8)</td>
<td>0.0% (0)</td>
<td>0.02</td>
<td>n.e.</td>
</tr>
<tr>
<td>Off treatment day 1–7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>7.3% (221)</td>
<td>6.2% (124)</td>
<td>3.2% (34)</td>
<td>0.000005</td>
<td>0.46 [0.33–0.64]</td>
</tr>
<tr>
<td>Death</td>
<td>2.1% (63)</td>
<td>1.9% (39)</td>
<td>0.5% (5)</td>
<td>0.004</td>
<td>0.23 [0.10–0.52]</td>
</tr>
<tr>
<td>MI</td>
<td>2.1% (63)</td>
<td>1.2% (25)</td>
<td>1.1% (12)</td>
<td>0.1</td>
<td>0.64 [0.35–1.15]</td>
</tr>
</tbody>
</table>

*Primary end point was a composite of death, MI, or urgent revascularization. Data are presented as percentages, with absolute event rates in parentheses. *p value and risk ratio of UFH plus ShortEnox versus LongEnox.

CI = confidence interval; LongEnox = long-term enoxaparin group; MI = myocardial infarction; n.e. = not estimable; ShortEnox = short-term enoxaparin group; UFH = unfractionated heparin group.
were different from the short treatment groups with respect to several baseline characteristics (Table 2). However, the TIMI risk score, which has been shown to predict events in this particular population, was equal among the treatment groups, indicating that the overall risk is not lower in patients continuing into the chronic phase (Table 1).

A possible cause for this early rebound phenomenon is remaining coronary thrombus, posing a threat for recurrent occlusion. This hypothesis is supported by a study by van Belle et al. (11), visualizing angiographically thrombus material in the coronary artery up to four weeks after hospital admission for MI.

Platelet activation may be important for the occurrence of early rebound. Clot-bound thrombin is a potent trigger for platelet activation and thrombus growth. Aspirin reduces the risk of rebound (1); however, early rebound does occur in acetylsalicylic acid-treated patients (2,4). More aggressive platelet inhibition with glycoprotein IIb/IIIa inhibitors further lowers the risk of rebound events in ACS patients (9).

Other mechanisms that could lead to a transient hypercoagulable state include depletion of natural anticoagulants such as tissue-factor pathway inhibitor and antithrombin (12–17). This is supported by the highly increased thrombin generation and activation markers observed 3 to 24 h after both UFH and LMWH treatment cessation, with prothrombin fragments 1 + 2 levels exceeding pretreatment prothrombin fragments 1 + 2 levels (18). This observation suggests a drug-related phenomenon of thrombin generation as opposed to a return to the natural course after treatment cessation. However, the fact that no early recurrences were observed after discontinuation of long-term enoxaparin suggests that this drug-related phenomenon is dependent on the activity of the underlying thrombotic process.

Whether these results imply that treatment with UFH or LMWH should be continued beyond the short-term regimen is unclear. Several ACS studies, including the TIMI 11B study, examined the possible benefit of prolonged LMWH treatment (7,19,20). Results were consistent and showed no benefit. However, a selection of ACS patients do benefit from prolonged anticoagulation treatment as shown in a recent study (21). High-risk patients, based on elevated troponin T levels and ST-segment deviation on admission, showed a clear and significant reduction in death or MI during the 90-day treatment period compared with short-term LMWH. Unfortunately, this treatment effect was gradually lost after LMWH was discontinued, resulting in equal rates of death or MI at one-year follow-up. Our study indicates that most benefit from prolonged treatment may be obtained in patients with three or more risk factors (Fig. 3). However, these patients represent approximately 65% of the total group.

The lack of efficacy in long-term LMWH treatment may also be related to the patient's compliance during home treatment (22). In the Fragmin during Instability in Coronary Artery Disease (FRISC) II study, anti-factor Xa measurements during follow-up showed a steady decline, dropping from 0.6 U/ml at the start to 0.4 U/ml at three months, with 29% of the patients showing levels smaller than 0.2 U/ml. Thus, a substantial proportion of patients had subtherapeutic levels during home treatment.

Several strategies may potentially reduce the incidence of recurrent ischemic events. First, gradual weaning of the dose of the anticoagulant has been shown to decrease the extent of rebound coagulation (14). Second, clinicians may decide not to discharge or transfer a patient until at least 24 h after drug discontinuation, particularly in high-risk subgroups.

Third, as rebound thrombin generation peaks between 6 and 12 h after discontinuation (18), it may be advisable to stop UFH infusion early in the morning in order to manage possible recurrences during daytime. Similarly, by scheduling the last LMWH dose in the evening, a fall in drug levels below the therapeutic range will occur in the morning. However, these recommendations have not been tested prospectively.

Study limitations. This study has several limitations. This was a post hoc analysis using prospectively acquired data, which focused on a selection of the total included patient population from the TIMI 11B and ESSENCE studies. A total of 983 (14%) patients were not included in the rebound analysis; 14% of the UFH group patients, 16% of the ShortEnox group patients, and 9% of the LongEnox group were excluded (Table 1). A significant proportion of exclusions consisted of patients in whom a revascularization was performed within 48 h after treatment cessation without recurrent anginal symptoms. The decision to revascularize these patients was apparently made on other clinical grounds during heparin treatment, and these patients were switched to open-label UFH before the intervention. Potentially, the benefits of revascularization versus a conservative approach, as demonstrated in recent randomized trials (23–25) could be explained by a reduction in rebound thrombotic events. However, because of selection bias and differences in pharmacologic treatments, this cannot be established from our data. The incidence of death or MI during the first four days after randomization was similar between the included and excluded patients.

The different stopping time for UFH and enoxaparin was based on the markedly longer therapeutic anticoagulant effect of enoxaparin as compared with UFH. After the last administration of enoxaparin, anti-Xa plasma levels remain in the therapeutic range between 12 and 15 h, whereas cessation of intravenous UFH is rapidly cleared after the infusion is stopped, resulting in nearly undetectable anti-Xa levels at 3 h (18).

Conclusions. Recurrent ischemic events were observed in a significant proportion of patients early after discontinuation of UFH and LMWH treatment. The majority of these events occurred within 24 h, and clinical predictors may identify patients at high risk. Continuing (fixed-dose) ad-
ministration of LMWH may prevent these early recurrences, especially in high-risk groups.

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