Therapy of Coronary Artery Disease

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

Abbreviations and Acronyms

ACS	= acute coronary syndromes
CI	= confidence interval
ESSENCE	= Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events
LMWH	= low-molecular-weight heparin
LongEnox	= long-term out-hospital continuation of enoxaparin treatment
MI	= myocardial infarction
OR	= odds ratio
ShortEnox	= short-term in-hospital enoxaparin treatment
TIMI	= Thrombolysis In Myocardial Infarction
UFH	= unfractionated heparin

(TIMI) 11B (7) trials and calculated in a per patient analysis the incidence of ischemic events after discontinuation of either UFH or enoxaparin. The prolonged fixed-dose LMWH treatment arm of the TIMI 11B trial allowed us to study the effect of this regimen on rebound phenomena.

METHODS

Protocol and patient population of the TIMI 11B and ESSENCE studies. The study protocols have been described in previous publications (6,7). In short, patients with unstable angina or non–Q-wave infarction, presenting within 24 h after onset of symptoms, were eligible for inclusion. A total of 7,081 patients were randomized, in a double dummy design, to intravenous UFH (n = 3,521) or subcutaneous enoxaparin (n = 3,560). In both studies, UFH treatment was continued for at least three days with a maximum of eight days. In both studies, enoxaparin was administered at a dose of 1 mg/kg twice a day and was continued until day 8 or hospital discharge. The TIMI 11B protocol required continuation of enoxaparin treatment with a fixed dose of 60 mg twice a day until day 43. All patients received aspirin 100 to 325 mg/day.

Principal results of the TIMI 11B and ESSENCE studies. The end points of the separate TIMI 11B and ESSENCE studies, as well as the combined end points of

these studies have been published previously (6–8). Treatment with enoxaparin resulted in a 20% reduction of the composite end point death or non-fatal MI, with an absolute reduction from 5.3% to 4.1% by day 8 (odds ratio [OR] = 0.77; confidence interval [CI] 0.62 to 0.95) and from 8.6% to 7.1% by day 43 (OR = 0.82; CI 0.69 to 0.97). The treatment benefit of enoxaparin over UFH occurred rapidly after the start of treatment with a significant end point reduction as early as day 2 after randomization. Enoxaparin and UFH showed a similar rate of major hemorrhage (approximately 1.2%) although a higher rate of minor hemorrhage was observed with enoxaparin treatment (10% vs. 4.3%).

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 1. Patient Selection for Current Analysis

	Treatment Group			
Randomized	**UFH** **N = 3,521**	**ShortEnox** **N = 2,381**	**LongEnox** **N = 1,179**	**Total** **N = 7,081**
Exclusion				
Treatment >14 days	n = 1	n = 2	n = 2	N = 5
Treatment duration missing	n = 25	n = 15	n = 1	N = 41
Revascularization during Rx	n = 102	n = 93	n = 44	N = 239
Revascularization <48 h after Rx without angina	n = 367	n = 231	n = 55	N = 653
Oral anticoagulants	n = 13	n = 14	n = 2	N = 29
Death during Rx	n = 1	n = 15	n = 0	N = 16
Total exclusion	n = 509	n = 370	n = 104	N = 983
Total inclusion	n = 3,012	n = 2,011	n = 1,075	N = 6,098

LongEnox = long-term enoxaparin; Rx = treatment; ShortEnox = short-term enoxaparin; UFH = unfractionated heparin.

Table 2. Characteristics of Study Patients Treated With UFH and Enoxaparin for At Least 48 h but ≤14 Days

Characteristics	Treatment Group			p Value
	UFH (n = 3,012)	ShortEnox (n = 2,011)	LongEnox (n = 1,075)	
Age (yrs)	64.4	63.9	63.7	0.2
Male (%)	63.9	64.3	68.1	0.04
Family history of CAD (%)	38.2	39.7	34.7	0.02
Current smoker (%)	25.5	25.4	26.7	0.7
History of hypertension (%)	51.3	52.8	47.8	0.03
History of hypercholesterolemia (%)	36.2	41.3	34.5	<0.001
History of diabetes (%)	20.9	20.8	22.5	0.5
Previous myocardial infarction (%)	39.6	41.3	32.7	<0.001
Previous aspirin use (%)	75.3	69.6	82.1	<0.001
Previous beta-blocker use (%)	38.4	37.5	34.3	<0.06
Median acute, in-hospital treatment duration (days + 25th/75th percentile)	3.0 (2.2/3.8)	3.4 (2.5/5.1)	5.8 (3.9/7.2)	<0.0001
Mean TIMI risk score	3.1	2.9	3.4	0.0001
TIMI risk factors distribution (%)				
0–2	33	40	23	
3–4	55	51	59	} <0.001
5–7	12	9	18	

CAD = coronary artery disease; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

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
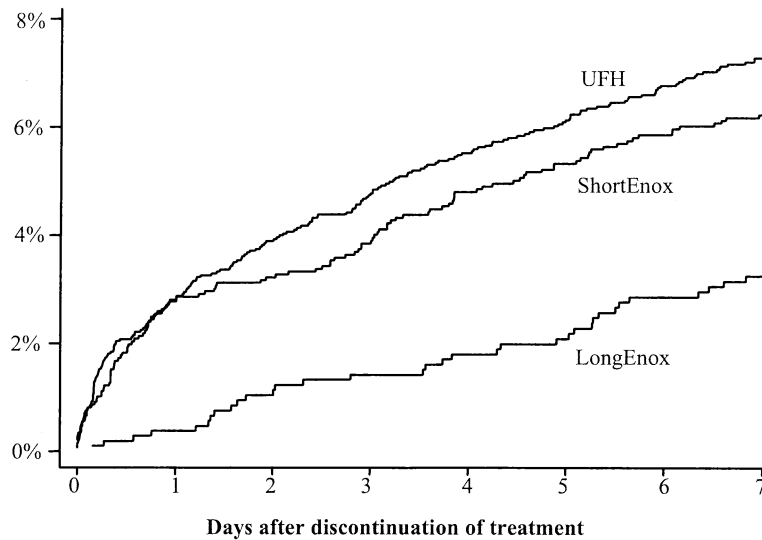
Figure 1. Cumulative incidence for the occurrence of death, myocardial infarction, or urgent revascularization by treatment group during the first seven days after treatment discontinuation. LongEnox = long-term out-hospital continuation of enoxaparin treatment; ShortEnox = short-term in-hospital enoxaparin treatment; UFH = unfractionated heparin.

higher incidence of ischemic events compared with the LongEnox group (UFH vs. LongEnox, p < 0.0001; Short-Enox 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 that 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

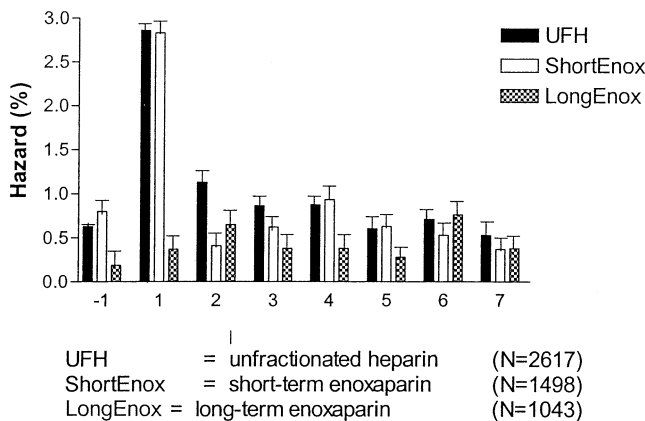rebound in the UFH and ShortEnox groups was also observed for the separate end points death and MI (Table 3).

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

Figure 2. Hazard of death, myocardial infarction, or urgent revascularization per day during the day before (−1) and days (1 to 7) after discontinuation of UFH or short-term enoxaparin. Note: by definition, day −1 (i.e., 24 h before treatment discontinuation) does not include patients who died or underwent an urgent revascularization. Abbreviations as in Figure 1.

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

	Treatment Group				
	UFH (n = 3,012)	ShortEnox (n = 2,011)	LongEnox (n = 1,075)	p Value*	Risk Ratio [95% CI]*
On treatment day −1					
Primary	0.6% (19)	0.8% (6)	0.2% (2)	0.2	0.37 [0.09–1.49]
Off treatment day 1					
Primary	2.9% (86)	2.8% (57)	0.4% (4)	0.000005	0.13 [0.06–0.30]
Death	0.9% (26)	0.8% (17)	0.1% (1)	0.007	0.16 [0.02–0.55]
MI	0.6% (17)	0.4% (8)	0.0% (0)	0.02	n.e.
Off treatment day 1–7					
Primary	7.3% (221)	6.2% (124)	3.2% (34)	0.000005	0.46 [0.33–0.64]
Death	2.1% (63)	1.9% (39)	0.5% (5)	0.0004	0.23 [0.10–0.52]
MI	2.1% (63)	1.2% (25)	1.1% (12)	0.1	0.64 [0.35–1.15]

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.

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 = 33). 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 isch-

Figure 3. The Thrombolysis In Myocardial Infarction (TIMI) risk factor distribution in patients with early rebound, that is, occurrence of a primary end point event within 24 h after discontinuation of treatment. Abbreviations as in Figure 1.

emic 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.
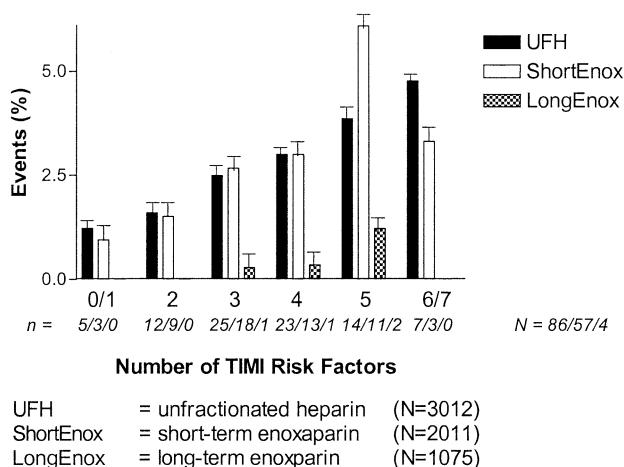
Patients continuing to chronic-phase LMWH treatment

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 angioscopically 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.

REFERENCES

1. Theroux P, Waters D, Lam J, Juneau M, McCans J. Reactivation of unstable angina after the discontinuation of heparin. N Engl J Med 1992;327:141–5.
2. Granger CB, Hirsch J, Califf RM, et al. Activated partial thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction: results from the GUSTO-I trial. Circulation 1996; 93:870–8.
3. Goodman SG, Barr A, Sobtchouk A, et al. Low molecular weight heparin decreases rebound ischemia in unstable angina or non–Q-wave myocardial infarction: the Canadian ESSENCE ST-segment monitoring substudy. J Am Coll Cardiol 2000;36:1507–13.
4. Bahit MC, Topol EJ, Califf RM, et al. Reactivation of ischemic events in acute coronary syndromes: results from GUSTO-IIb. Global Use of Strategies To Open occluded arteries in acute coronary syndromes. J Am Coll Cardiol 2001;37:1001–7.
5. Fragmin during Instability in Coronary Artery Disease (FRISC) Study Group. Low-molecular-weight heparin during instability in coronary artery disease. Lancet 1996;347:561–8.
6. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events Study Group. N Engl J Med 1997;337:447–52.
7. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non–Q-wave myocardial infarction: results of the Thrombolysis In Myocardial Infarction (TIMI) 11B trial. Circulation 1999;100:1593–601.
8. Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of enoxaparin for unstable angina/non–Q-wave myocardial infarction: TIMI 11B-ESSENCE meta-analysis. Circulation 1999; 100:1602–8.
9. Lauer MA, Houghtaling PL, Peterson JG, et al. Attenuation of rebound ischemia after discontinuation of heparin therapy by glycoprotein IIb/IIIa inhibition with eptifibatide in patients with acute coronary syndromes: observations from the Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial. Circulation 2001;104:2772–7.
10. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non–ST-elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000;284:835–42.
11. Van Belle E, Lablanche JM, Bauters C, et al. Coronary angioscopic findings in the infarct-related vessel within 1 month of acute myocardial infarction: natural history and the effect of thrombolysis. Circulation 1998;97:26–33.
12. Granger CB, Miller JM, Bovill EG, et al. Rebound increase in thrombin generation and activity after cessation of intravenous heparin in patients with acute coronary syndromes. Circulation 1995;91: 1929–5.
13. Gold HK, Torres FW, Garabedian HD, et al. Evidence for a rebound coagulation phenomenon after cessation of a 4-hour infusion of a specific thrombin inhibitor in patients with unstable angina pectoris. J Am Coll Cardiol 1993;21:1039–47.
14. Becker RC, Spencer FA, Li Y, et al. Thrombin generation after the abrupt cessation of intravenous unfractionated heparin among patients with acute coronary syndromes: potential mechanisms for heightened prothrombotic potential. J Am Coll Cardiol 1999;34:1020–7.
15. Linder R, Oldgren J, Egberg N, et al. The effect of a low molecular mass thrombin inhibitor, inogatran, and heparin on thrombin generation and fibrin turnover in patients with unstable coronary artery disease. Eur Heart J 1999;20:506–18.
16. Flather MD, Weitz JI, Yusuf S, et al. Reactivation of coagulation after stopping infusions of recombinant hirudin and unfractionated heparin in unstable angina and myocardial infarction without ST elevation: results of a randomized trial. Eur Heart J 2000;21:1473–81.
17. Hansen JB, Sandset PM. Differential effects of low molecular weight heparin and unfractionated heparin on circulating levels of antithrombin and tissue factor pathway inhibitor (TFPI): a possible mechanism for difference in therapeutic efficacy. Thromb Res 1998;91:177–81.
18. Bijsterveld NR, Moons AH, Meijers JC, et al. Rebound thrombin generation after heparin therapy in unstable angina: a randomized comparison between unfractionated and low-molecular-weight heparin. J Am Coll Cardiol 2002;39:811–7.
19. The FRISC Investigators. Low-molecular-weight heparin during instability in coronary artery disease: Fragmin during Instability in Coronary Artery Disease (FRISC) study group. Lancet 1996;347: 561–8.
20. The FRAXIS Investigators. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non–Q-wave myocardial infarction: FRAX.I.S. (FRAxiparine in Ischaemic Syndrome). Eur Heart J 1999;20:1553–62.
21. Lindahl B, Diderholm E, Lagerqvist B, Wallentin L. Effect on mortality by low heparin in relation to STT changes and level of troponin T in unstable coronary artery disease—a FRISC II substudy (abstr II). Circulation 2000;102:591.
22. Wallentin L, Siegbahn A, Diderholm E. Lower anti-Xa levels after 6 weeks might contribute to the late loss of benefit of long-term low-molecular weight heparin (dalteparin) treatment in the FRISC2 medical trial. Eur Heart J 2000;Suppl 21:P1098.
23. Cannon CP, Weintraub WS, Demopoulos LA, Robertson DH, Gormley GJ, Braunwald E. Invasive versus conservative strategies in unstable angina and non–Q-wave myocardial infarction following treatment with tirofiban: rationale and study design of the international TACTICS-TIMI 18 trial. Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy. Thrombolysis In Myocardial Infarction. Am J Cardiol 1998;82:731–6.
24. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Lancet 1999;354:708–15.
25. Fox KA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina or non–ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. Lancet 2002;360:743–51.