

## 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

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**Background**—Low-molecular-weight heparins are attractive alternatives to unfractionated heparin (UFH) for management of unstable angina/non-Q-wave myocardial infarction (UA/NQMI).

**Methods and Results**—Patients (n=3910) with UA/NQMI were randomized to intravenous UFH for  $\geq 3$  days followed by subcutaneous placebo injections or uninterrupted antithrombin therapy with enoxaparin during both the acute phase (initial 30 mg intravenous bolus followed by injections of 1.0 mg/kg every 12 hours) and outpatient phase (injections every 12 hours of 40 mg for patients weighing  $< 65$  kg and 60 mg for those weighing  $\geq 65$  kg). The primary end point (death, myocardial infarction, or urgent revascularization) occurred by 8 days in 14.5% of patients in the UFH group and 12.4% of patients in the enoxaparin group (OR 0.83; 95% CI 0.69 to 1.00;  $P=0.048$ ) and by 43 days in 19.7% of the UFH group and 17.3% of the enoxaparin group (OR 0.85; 95% CI 0.72 to 1.00;  $P=0.048$ ). During the first 72 hours and also throughout the entire initial hospitalization, there was no difference in the rate of major hemorrhage in the treatment groups. During the outpatient phase, major hemorrhage occurred in 1.5% of the group treated with placebo and 2.9% of the group treated with enoxaparin ( $P=0.021$ ).

**Conclusions**—Enoxaparin is superior to UFH for reducing a composite of death and serious cardiac ischemic events during the acute management of UA/NQMI patients without causing a significant increase in the rate of major hemorrhage. No further relative decrease in events occurred with outpatient enoxaparin treatment, but there was an increase in the rate of major hemorrhage. (*Circulation*. 1999;100:1593-1601.)

**Key Words:** angina ■ heparin ■ anticoagulants ■ coronary disease

After rupture of a vulnerable atherosclerotic plaque in a coronary artery, tissue factor in the lipid-rich core is exposed and complexes with factor VIIa, and the tissue factor-factor VIIa complex then promotes generation of factor Xa.<sup>1,2</sup> Owing to a multiplier effect in the coagulation cascade, relatively low concentrations of factor Xa lead to the downstream production of large quantities of thrombin, with ultimate deposition of fibrin strands, as well as activation of platelets.<sup>3,4</sup> Clinical studies<sup>5</sup> suggest that patients with an acute coronary syndrome who demonstrate biochemical evidence of activation of the coagulation cascade are at increased risk of clinical events. Also, as reported by Merlini et al,<sup>6</sup> there is persistent activation of the coagulation cascade for several weeks to months after the index event, which has

led investigators to design antithrombotic treatments that can be administered on a long-term basis. Antithrombotic strategies for the acute management of patients with unstable angina/non-Q-wave myocardial infarction (MI) include a combination of an antithrombin agent, usually an intravenous infusion of unfractionated heparin, and an antiplatelet agent, usually oral aspirin.<sup>7-12</sup> Beyond aspirin, optimal outpatient-phase therapy for patients presenting with unstable angina/non-Q-wave MI remains to be defined.<sup>13</sup>

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Low-molecular-weight heparin preparations are theoretically attractive alternatives to intravenous unfractionated heparin because of an enhanced anti-factor-Xa:anti-factor-

Received April 14, 1999; revision received July 23, 1999; accepted July 26, 1999.

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Ila ratio, leading to reductions in both thrombin generation and thrombin activity, a reliable anticoagulant effect, without the need for monitoring of the activated partial thromboplastin time (aPTT), and they provide a simpler method of administration via the subcutaneous route, permitting both short- and long-term treatment.<sup>14–17</sup> Previous studies have shown that dalteparin, when added to aspirin, was superior to placebo but similar to unfractionated heparin for prevention of death and MI in patients with unstable angina/non-Q-wave MI.<sup>18,19</sup> The ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events) study reported that a brief course of therapy (median duration of treatment 2.6 days) of subcutaneous injections of enoxaparin 1.0 mg/kg every 12 hours was superior to intravenous unfractionated heparin in patients with unstable angina/non-Q-wave MI.<sup>20</sup>

The TIMI 11A trial, a dose-ranging study, demonstrated that an initial 30-mg intravenous bolus followed by subcutaneous injections of 1.0 mg/kg enoxaparin every 12 hours was associated with a major hemorrhage rate of 1.9%, whereas a higher dose of 1.25 mg/kg every 12 hours was associated with a major hemorrhage rate of 6.5%.<sup>21</sup> Through 14 days, the incidence of death, recurrent MI, or recurrent myocardial ischemia requiring revascularization was 5.2% in the 1.0 mg/kg dose group and 5.6% in the 1.25 mg/kg dose group.<sup>21</sup> Thus, an enoxaparin dose of 1.0 mg/kg was associated with a lower risk of major hemorrhage without an apparent loss of efficacy. Having identified a safe and effective dose of enoxaparin, we designed the TIMI 11B trial to test the benefits of a strategy of an extended course of uninterrupted antithrombotic therapy with enoxaparin compared with standard treatment with unfractionated heparin for prevention of death and cardiac ischemic events in patients with unstable angina/non-Q-wave MI.

## Methods

### Patient Population

Patient enrollment occurred between August 1996 and March 1998 in 200 centers across 10 countries in North America, South America, and Europe. All patients were required to have ischemic discomfort of  $\geq 5$  minutes' duration at rest within 24 hours before randomization and additional evidence of ischemic heart disease as described below. At the start of the trial, patients were eligible if they had either a history of coronary artery disease (as evidenced by an abnormal coronary angiogram, prior MI, CABG surgery, or PTCA), ST deviation, or elevated serum cardiac markers. After 10 months and enrollment of  $\approx 1800$  patients, the Operations Committee performed a blinded review of the aggregate event rate and made the decision to modify the inclusion criteria to focus on higher-risk patients by requiring that all patients have either ST deviation or positive serum cardiac markers. Before the change in enrollment criteria, 731 patients were enrolled solely on the basis of a prior history of coronary artery disease. The major exclusion criteria were as follows: planned revascularization within 24 hours, a treatable cause of angina, an evolving Q-wave MI, a history of CABG surgery within 2 months or PTCA within 6 months, treatment with a continuous infusion of unfractionated heparin for  $>24$  hours before enrollment, history of heparin-associated thrombocytopenia with or without thrombosis, and contraindications to anticoagulation. The protocol was approved by the institutional review board at each enrolling site, and written informed consent was obtained from patients before randomization.

### Study Protocol

There were 2 treatment phases during the trial: (1) an acute phase designed to determine whether treatment with enoxaparin was superior to unfractionated heparin for preventing events during the initial hospitalization and for a short period thereafter, and (2) an outpatient phase that sought to explore whether there was a potential benefit to administration of enoxaparin for an additional 35 days after hospital discharge.

All patients received aspirin (100 to 325 mg/d) and were randomized to 1 of 2 antithrombin strategies. All patients received both an intravenous infusion (unfractionated heparin or matched placebo) and subcutaneous injections (enoxaparin or matched placebo) in a double-blind fashion. The standard antithrombin strategy was a weight-adjusted regimen of unfractionated heparin for a minimum of 3 days (and maximum of 8 days at the treating physician's discretion) beginning with a bolus of 70 U/kg and an initial infusion of  $15 \text{ U} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . The requirement of  $\geq 3$  days of treatment with unfractionated heparin was incorporated into the protocol to match the design of previously reported trials demonstrating the benefit of intravenous unfractionated heparin in similar patient populations.<sup>7,13</sup> The aPTT was measured at baseline, 4 to 6 hours after initiation of study drug, and then as indicated per a preapproved nomogram at each institution designed to maintain a target aPTT of 1.5 to 2.5 times control. To maintain the double-blind design, the aPTT results were reported to an unblinded third party who was not involved in the patient's care and who ordered adjustments to the intravenous infusion based on the actual aPTT value for patients receiving active unfractionated heparin or a mock value for patients receiving placebo infusions. The investigational antithrombin strategy was enoxaparin (supplied by Rhône-Poulenc Rorer, Collegeville, Pa) given as an initial intravenous bolus of 30 mg followed by immediate initiation of subcutaneous injections of 1 mg/kg (100 anti-factor Xa units per kilogram) every 12 hours. Double-blind subcutaneous injections were continued until hospital discharge or day 8, whichever came first.

Patients could undergo diagnostic catheterization at the treating physician's discretion and receive either double-blind study drug, no anticoagulation, or open-label intravenous unfractionated heparin. All interventional coronary procedures were performed with open-label, unfractionated heparin after an activated clotting time of  $\geq 350$  seconds had been achieved. For patients scheduled for CABG surgery, study therapy was discontinued 12 hours before the operation.

Patients who completed the acute phase were eligible for enrollment in the outpatient phase unless they underwent CABG surgery, had no clinically significant coronary artery disease, sustained a major hemorrhage, developed severe thrombocytopenia, had another indication for chronic anticoagulation, or withdrew consent. Patients who had originally been assigned to intravenous unfractionated heparin received placebo subcutaneous injections twice daily. Those patients originally assigned to enoxaparin received subcutaneous injections every 12 hours of 40 mg of enoxaparin if they weighed  $<65$  kg and 60 mg of enoxaparin if they weighed  $\geq 65$  kg. Double-blind outpatient-phase therapy continued through day 43.

### Study End Points

The primary efficacy end point was a composite of all-cause mortality, recurrent MI, or urgent revascularization. Comparison of treatments received during the acute phase was ascertained at 8 days, and assessment of the incremental benefit of the outpatient phase was ascertained at 43 days. Additional prespecified time points for comparison of the 2 treatment groups were 48 hours and 14 days.

An MI was considered to be present at enrollment if any of the following criteria were met: (1) creatine kinase-MB (CKMB) was greater than normal ( $\geq 3\%$  of total CK) at baseline and 8 hours after enrollment; (2) CKMB was elevated at the 16-hour sample and no ischemic discomfort of  $\geq 30$  minutes' duration occurred between enrollment and the 16-hour sample; (3) in the absence of CKMB measurements, total CK was elevated to  $>2$  times the upper limit of normal; and (4) ECGs obtained at  $\approx 8$  or 16 hours after enrollment

exhibited new significant ( $>0.03$  second) Q waves in  $\geq 2$  contiguous leads that were not present on the enrollment ECG.

The definition of an MI after enrollment required that either of the following criteria be met:

1. CKMB was elevated above normal and increased by  $\geq 50\%$  over the previous value. In the absence of CKMB data, total CK had to be reelevated to  $>2$  times the upper limit of normal and increased by  $\geq 25\%$  over the previous value; if reelevated to  $<2$  times the upper limit of normal, total CK had to exceed the upper limit of normal by  $\geq 50\%$  and exceed the previous value by 2-fold. For patients who had PTCA  $<24$  hours previously, CKMB (or total CK if MB not available) had to be  $\geq 3$  times the upper limit of normal and increased by  $\geq 50\%$  of the previous value. For patients who had CABG surgery  $<24$  hours previously, CKMB (or CK if MB not available) had to be  $\geq 5$  times the upper limit of normal and increased by  $\geq 50\%$  of the previous value.
2. The ECG showed new significant ( $>0.03$  seconds) Q waves in  $\geq 2$  contiguous leads or new left bundle-branch block not seen on enrollment and not observed by 18 hours if the subject was classified as having an MI at enrollment.

Severe recurrent ischemia requiring urgent revascularization was defined as an episode of recurrent angina prompting the performance of coronary revascularization on the index hospitalization or an episode of recurrent angina after discharge that resulted in rehospitalization during which coronary revascularization was performed.

Secondary efficacy end points of interest included the individual elements of the primary end point and the composite of death or nonfatal MI.

The main safety end point was major hemorrhage, defined as overt bleeding resulting either in death; a bleed in a retroperitoneal, intracranial, or intraocular location; a hemoglobin drop of  $\geq 3$  g/dL; or the requirement of transfusion of  $\geq 2$  U of blood. Minor hemorrhage was any clinically important bleeding that did not qualify as major; for example, epistaxis, ecchymosis, hematoma, or macroscopic hematuria.

An independent Clinical Events Committee blinded to treatment assignment reviewed relevant ECG tracings, laboratory data, and narrative summaries of clinical events for the purposes of adjudicating all primary efficacy and safety end points.

## Statistical Analysis

Analysis of the primary efficacy end point was conducted on all randomized patients by the intention-to-treat principle. To adjust for country differences in treatment effect, a logistic regression model was used that included terms for country, treatment assignment, and their interaction. Significance of model terms was assessed by likelihood ratio  $\chi^2$  statistics with 2-sided probability values. ORs, 95% CIs, and relative risks were constructed for the primary end point as well as its composite elements arranged so that values  $<1$  indicated a benefit of enoxaparin. A secondary analysis was performed on the time to development of the first element of the primary efficacy end point in the 2 treatment groups by use of Kaplan-Meier methodology and a log-rank test. Comparison of baseline characteristics was by  $\chi^2$  analysis for categorical variables and either Student's *t* test or Wilcoxon signed rank test as appropriate for continuous variables.

The sample size of the trial was an event-based target such that a total of 650 patients were to have experienced  $\geq 1$  element of the primary efficacy end point through 43 days. No interim analyses were conducted during the course of the trial. The chairman of an independent Data Safety Monitoring Board (DSMB) received unblinded safety reports after successive groups of 300 patients were enrolled. No interim reports of efficacy were included with the above safety reports. After review of each safety report, the Operations Committee was notified whether any concerns had arisen. A meeting of the entire DSMB could be convened at the chairman's discretion. Throughout the course of the trial, enrollment continued without any safety concerns, and the chairman did not convene any meetings of the full DSMB.

## Results

A total of 3910 patients were enrolled, with 1957 patients assigned to unfractionated heparin and 1953 to enoxaparin. The 2 treatment groups were well matched for baseline characteristics (Table 1). Of note, the profile of the patients enrolled in the trial was typical of patients presenting with a severe acute coronary syndrome in that 20% were diabetic, nearly 33% had sustained a prior MI, ischemic discomfort occurred despite previous treatment with aspirin in almost 85%, nearly 75% of the population presented with ST deviation on the ECG, and 40% had elevated serum cardiac markers. Approximately 60% of patients were diagnosed as having unstable angina, 35% with a non-Q-wave MI and 4% with an evolving Q-wave MI.

Double-blind study-drug therapy was initiated in 99% of patients. The median (interquartile range) duration of acute-phase therapy in the group assigned to unfractionated heparin was 3.0 (2.99, 3.98) days and by protocol design was longer in the enoxaparin group at 4.6 (2.97, 6.59) days. The median durations of treatment with the placebo intravenous and placebo subcutaneous therapies were 3.0 and 4.6 days, respectively, which were identical to those for the active therapies. In the group assigned to unfractionated heparin, the aPTT was between 55 and 85 seconds in 26% of patients within 6 to 12 hours and ranged between 42% and 47% of patients within 12 to 96 hours. Over the same time intervals, the aPTT was  $<60$  seconds in 96% of patients assigned to enoxaparin.

Kaplan-Meier estimates of the composite primary end point of death, MI, or urgent revascularization through the first 72 hours are shown in Figure 1. This corresponds to the period when both study groups were receiving antithrombin therapy. The curves began to separate by 8 hours. By 48 hours, the event rate was 7.3% in the unfractionated heparin group versus 5.5% in the enoxaparin group (OR 0.75; 95% CI 0.58 to 0.97;  $P=0.026$ ). This corresponds to a 23.8% reduction in the relative risk of the primary end point and was the largest treatment effect observed during the course of the trial (Table 2).

At 8 days, the incidence of the primary end point was 14.5% in the unfractionated heparin group and 12.4% in the enoxaparin group (OR 0.83; 95% CI 0.69 to 1.00;  $P=0.048$ ) (Figure 2). On the basis of the differences in the composite end point, 21 events would be avoided per 1000 patients treated with enoxaparin. For each element of the end point, there was a reduction in events in the group assigned to enoxaparin (Table 2). Similarly, the rate of the composite double end point of death or MI was reduced from 5.9% in the unfractionated heparin group to 4.6% in the enoxaparin group (OR 0.77; 95% CI 0.58 to 1.02;  $P=0.073$ ).

A stable treatment benefit of enoxaparin was observed through 14 days, at which time the incidence of the primary end point was 16.7% in the unfractionated heparin group and 14.2% in the enoxaparin group (OR 0.82; 95% CI 0.69 to 0.98;  $P=0.029$ ) (Figure 2). The event rates for each element of the primary end point and for the composite of death and MI also were lower in the enoxaparin group through 14 days (Table 2). There was no evidence of an abrupt increase in the

**TABLE 1. Baseline Characteristics of Study Patients**

| Characteristics  | Treatment Group          |                        |  |                        |
|--|--------------------------|------------------------|--|------------------------|
|  | At Initial Randomization |                        | At Start of Outpatient-Treatment Phase |                        |
|  | UFH<br>(n=1957)          | Enoxaparin<br>(n=1953) | UFH<br>(n=1185)                        | Enoxaparin<br>(n=1179) |
| Age, y   | 66 (57, 72)              | 65 (56, 73)            | 66 (57, 72)                            | 65 (55, 72)            |
| Weight, kg   | 77 (68, 87)              | 77 (68, 86)            | 78 (68, 88)                            | 78 (69, 88)            |
| Male sex   | 1256 (64.2)              | 1276 (65.3)            | 790 (66.7)                             | 804 (68.2)             |
| Risk factors for CAD   |                          |                        |  |                        |
| Family history   | 667 (34.1)               | 686 (35.1)             | 407 (34.3)                             | 412 (34.9)             |
| Hypertension   | 974 (49.8)               | 968 (49.6)             | 566 (47.8)                             | 560 (47.5)             |
| Hypercholesterolemia   | 619 (31.6)               | 661 (33.8)             | 365 (30.8)                             | 415 (35.2)             |
| Diabetes mellitus  | 393 (20.1)               | 385 (19.7)             | 229 (19.3)                             | 258 (21.9)             |
| Current smoker   | 527 (26.9)               | 521 (26.7)             | 321 (27.1)                             | 315 (26.7)             |
| Prior cardiac history  |                          |                        |  |                        |
| Angina before current episode  | 1125 (57.5)              | 1106 (56.6)            | 664 (56.0)                             | 652 (55.3)             |
| Positive cardiac catheterization*                                    | 516 (26.4)               | 512 (26.2)             | 321 (27.1)                             | 334 (28.3)             |
| Positive ETT   | 270 (13.8)               | 277 (14.2)             | 156 (13.2)                             | 181 (15.4)             |
| MI   | 633 (32.3)               | 607 (31.1)             | 393 (33.2)                             | 383 (32.5)             |
| CABG   | 258 (13.2)               | 267 (13.7)             | 169 (14.3)                             | 191 (16.2)             |
| PTCA   | 232 (11.9)               | 223 (11.4)             | 149 (12.6)                             | 144 (12.2)             |
| ECG changes†   | 83%                      | 83%                    | 82%                                    | 82%                    |
| ST-segment elevation   | 533 (27.2)               | 515 (26.4)             | 315 (26.6)                             | 301 (25.5)             |
| ST-segment depression  | 1081 (55.2)              | 1069 (54.7)            | 613 (51.7)                             | 635 (53.9)             |
| Any ST deviation   | 1415 (72.3)              | 1400 (71.7)            | 825 (69.6)                             | 836 (70.9)             |
| T-wave inversion   | 852 (43.5)               | 794 (40.7)             | 513 (43.3)                             | 473 (40.1)             |
| No ECG changes   | 330 (16.9)               | 342 (17.5)             | 217 (18.3)                             | 211 (17.9)             |
| Time from qualifying discomfort to first dose of study medication, h | 11.0 (5.9, 18.9)         | 10.9 (5.8, 18.5)       | 11.5 (6.1, 19.8)                       | 11.5 (6.0, 19.0)       |
| Previous therapy   |                          |                        |  |                        |
| Aspirin treatment within prior 7 days                                | 1651 (84.4)              | 1624 (83.2)            | 1013 (85.5)                            | 978 (83.0)             |
| IV UFH $\leq$ 24 hours before randomization                          | 676 (34.5)               | 653 (33.4)             | 434 (36.6)                             | 410 (34.8)             |
| Elevated serum cardiac markers                                       | 774 (39.6)               | 738 (37.8)             | 472 (39.8)                             | 460 (39.0)             |
| Final diagnosis of presenting symptoms                               |                          |                        |  |                        |
| Unstable angina  | 1136 (58.0)              | 1153 (59.0)            | 721 (60.8)                             | 717 (60.8)             |
| Non-Q-wave MI  | 676 (34.5)               | 658 (33.7)             | 424 (35.8)                             | 415 (35.2)             |
| Q-wave MI  | 74 (3.8)                 | 69 (3.5)               | 31 (2.6)                               | 37 (3.1)               |

Data shown are n (%) for dichotomous variables and median (25th, 75th percentile) for continuous variables.

CAD indicates coronary artery disease; ETT, exercise tolerance test; and UFH, unfractionated heparin.

\*"Positive cardiac catheterization" indicates that coronary stenosis of  $\geq 50\%$  was observed.

†ECG subcategories are not mutually exclusive.

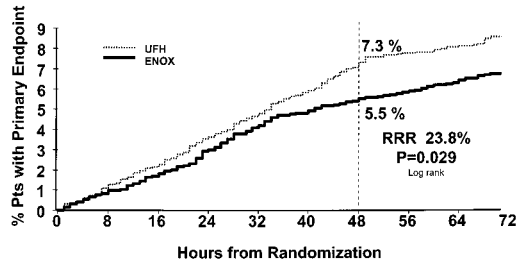
P=NS for all comparisons.

rate of events (ie, "rebound") within 24 hours of discontinuation of either study drug (Figure 2).

Differences in treatment effect with enoxaparin in several subgroups of interest based on characteristics of the patient's presenting illness are shown in Figure 3. With rare exceptions, such as no ECG changes at presentation, all subgroups had point estimates for the OR that favored enoxaparin. Noteworthy subgroups in which there was a particularly strong treatment benefit of enoxaparin were those patients who presented with various ECG changes or aspirin treatment within the preceding 24 hours.

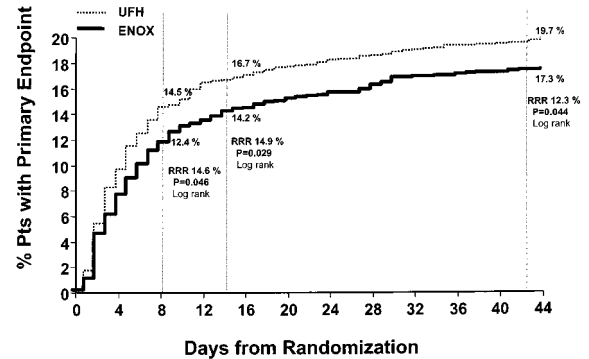
The number of patients who progressed to the outpatient phase was 1185 (60.6%) in the unfractionated heparin group and 1179 (60.4%) in the enoxaparin group. The major reasons patients did not enter the chronic phase were performance of CABG surgery (n=344 [8.8%]), informed consent withdrawal (n=349 [8.9%]), and an adverse event (eg, bleeding) (n=168 [4.3%]). The baseline characteristics of the cohorts from the 2 treatment groups that participated in the outpatient phase were well matched and were similar those seen in the full cohort at the original randomization (Table 1). As noted in Figure 2, the initial treatment benefit with enoxaparin





**Figure 1.** Kaplan-Meier plots of time to first event of primary end point of death, MI, or urgent revascularization over first few days of treatment when there is a direct comparison of intravenous unfractionated heparin (UFH) and subcutaneous enoxaparin (ENOX). RRR indicates relative risk reduction; Pts, patients.

observed through day 14 was sustained, but during the outpatient phase, the 2 curves remained parallel to each other, which suggests that there was no further relative treatment benefit of an additional 35 days of enoxaparin therapy. By 43 days, the incidence of the primary end point was 19.7% in the unfractionated heparin group and was reduced to 17.3% in the enoxaparin group (OR 0.85; 95% CI 0.72 to 1.00;  $P=0.048$ ). As was the case for observations at days 8 and 14, the event rates for each element of the primary end point and for the composite of death and MI also were lower in the enoxaparin



**Figure 2.** Kaplan-Meier plots of time to first event of primary end point through 43 days. Vertical dashed lines indicate comparisons at day 8 (end of acute phase), day 14 (for comparison with primary end point of ESSENCE trial), and day 43 (end of chronic phase). Abbreviations as in Figure 1.

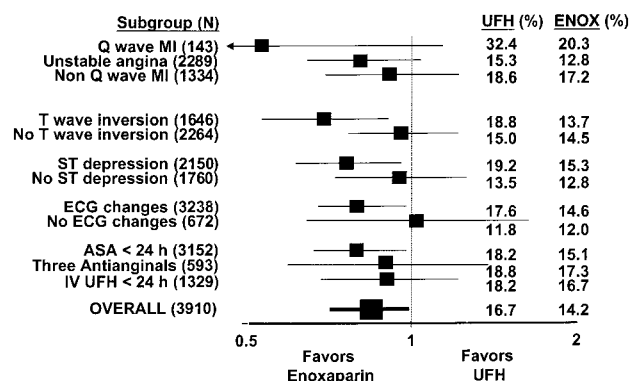
group (Table 2). Of note, the incidence of urgent revascularization was reduced from 12.6% in the unfractionated heparin group to 10.7% in the enoxaparin group (OR 0.82; 95% CI 0.67 to 1.00;  $P=0.050$ ), which represents a 15.6% reduction in the relative risk of that event.

Patients who had not experienced a primary end point event up to day 8 were analyzed to assess the incidence of the

**TABLE 2. Incidence of Primary End Point and Individual Elements for All Randomized Patients\***

| Time Point | End Point                         | Treatment Group                 |                     | Risk Reduction, % | OR (95% CI)      | P     |
|------------|-----------------------------------|---------------------------------|---------------------|-------------------|------------------|-------|
|            |                                   | Unfractionated Heparin (n=1957) | Enoxaparin (n=1953) |                   |                  |       |
| 48 h       | Death                             | 6 (0.3)                         | 11 (0.6)            | -83.7             | 1.84 (0.68-4.99) | 0.219 |
|            | MI                                | 38 (1.9)                        | 26 (1.3)            | 31.4              | 0.68 (0.41-1.13) | 0.129 |
|            | Urgent revascularization          | 103 (5.3)                       | 79 (4.0)            | 23.1              | 0.76 (0.56-1.02) | 0.068 |
|            | Death/MI                          | 42 (2.1)                        | 33 (1.7)            | 21.3              | 0.78 (0.49-1.24) | 0.292 |
|            | Death/MI/Urgent revascularization | 142 (7.3)                       | 108 (5.5)           | 23.8              | 0.75 (0.58-0.97) | 0.026 |
| 8 d        | Death                             | 41 (2.1)                        | 34 (1.7)            | 16.9              | 0.83 (0.52-1.31) | 0.421 |
|            | MI                                | 93 (4.8)                        | 66 (3.4)            | 28.9              | 0.70 (0.51-0.97) | 0.028 |
|            | Urgent revascularization          | 190 (9.7)                       | 167 (8.6)           | 11.9              | 0.87 (0.70-1.08) | 0.197 |
|            | Death/MI                          | 115 (5.9)                       | 90 (4.6)            | 21.6              | 0.77 (0.58-1.02) | 0.073 |
|            | Death/MI/Urgent revascularization | 284 (14.5)                      | 242 (12.4)          | 14.6              | 0.83 (0.69-1.00) | 0.048 |
| 14 d       | Death                             | 55 (2.8)                        | 43 (2.2)            | 21.7              | 0.78 (0.52-1.17) | 0.223 |
|            | MI                                | 105 (5.4)                       | 83 (4.2)            | 20.8              | 0.78 (0.58-1.05) | 0.099 |
|            | Urgent revascularization          | 217 (11.1)                      | 187 (9.6)           | 13.6              | 0.85 (0.69-1.04) | 0.111 |
|            | Death/MI                          | 135 (6.9)                       | 111 (5.7)           | 17.6              | 0.81 (0.62-1.05) | 0.114 |
|            | Death/MI/Urgent revascularization | 326 (16.7)                      | 277 (14.2)          | 14.9              | 0.82 (0.69-0.98) | 0.029 |
| 43 d       | Death                             | 78 (4.0)                        | 75 (3.8)            | 3.6               | 0.96 (0.69-1.33) | 0.810 |
|            | MI                                | 129 (6.6)                       | 107 (5.5)           | 16.9              | 0.82 (0.63-1.07) | 0.141 |
|            | Urgent revascularization          | 247 (12.6)                      | 208 (10.7)          | 15.6              | 0.82 (0.67-1.00) | 0.050 |
|            | Death/MI                          | 174 (8.9)                       | 155 (7.9)           | 10.7              | 0.88 (0.70-1.11) | 0.276 |
|            | Death/MI/Urgent revascularization | 385 (19.7)                      | 337 (17.3)          | 12.3              | 0.85 (0.72-1.00) | 0.048 |

\*A patient may have had  $\geq 1$  component event in a given period, but the composite end points are mutually exclusive counts with ranking of end point elements in the order shown.



**Figure 3.** OR plots of treatment effect of enoxaparin vs unfractionated heparin with respect to primary end point through 14 days in selected subgroups of patients based on characteristics of presenting illness. Point estimates of OR are shown with squares, and 95% CIs are depicted by width of horizontal lines. ASA indicates aspirin; ENOX, enoxaparin; and UFH, unfractionated heparin.

primary end point between day 8 and day 43 (outpatient phase). Of 1673 such patients in the unfractionated heparin group, 101 (6.0%) experienced an end point by day 43 compared with 95 (5.6%) of 1711 patients in the enoxaparin group (OR 0.91; 95% CI 0.69 to 1.22;  $P=0.55$ ).

Rates of major hemorrhage are summarized in Table 3 for the cohort of patients treated with double-blind study drug. During the first 72 hours and also throughout the entire initial hospitalization, there was no significant difference in the rate of major hemorrhage in the 2 treatment groups. During the outpatient phase, the rate of major hemorrhage was 1.5% in the group treated with placebo and 2.9% in the group treated with enoxaparin ( $P=0.021$ ). The excess of major hemorrhage in the enoxaparin group was almost equally split between spontaneous and instrumented events. At all time points, the rate of minor hemorrhage, which in the majority of cases was

**TABLE 3. Hemorrhagic Events for All Treated Patients**

|                                | Treatment Group*                   |                         |          |
|--------------------------------|------------------------------------|-------------------------|----------|
| Time Point                     | Unfractionated<br>Heparin (n=1936) | Enoxaparin*<br>(n=1938) | <i>P</i> |
| 72 h                           |                                    |                         |          |
| Major hemorrhage               | 14 (0.7)                           | 16 (0.8)                | 0.714    |
| Minor hemorrhage               | 45 (2.3)                           | 99 (5.1)                | <0.001   |
| End of initial hospitalization |                                    |                         |          |
| Major hemorrhage               | 19 (1.0)                           | 29 (1.5)                | 0.143    |
| Minor hemorrhage               | 48 (2.5)                           | 176 (9.1)               | <0.001   |
|                                | Placebo<br>(n=1185)                | Enoxaparin<br>(n=1179)  |          |
| Between day 8 and day 43       |                                    |                         |          |
| Major hemorrhage               | 18 (1.5)                           | 34 (2.9)                | 0.021    |
| Minor hemorrhage               | 62 (5.2)                           | 227 (19.3)              | <0.001   |

\*For comparison of hemorrhage events between day 8 and day 43, the numbers of patients treated with placebo injections and enoxaparin injections were 1185 and 1179, respectively. For all other comparisons, the values of 1936 and 1938 were used for patients treated with unfractionated heparin vs enoxaparin.

due to ecchymosis at the subcutaneous injection site or a hematoma at the site of a sheath inserted for cardiac catheterization, was significantly higher in the enoxaparin group. There were no significant differences in the rates of other adverse events such as stroke (unfractionated heparin 1.0%; enoxaparin 1.2%), transient ischemic attack (unfractionated heparin 0.3%; enoxaparin 0.3%), or thrombocytopenia  $<100\,000/\text{mm}^3$  (unfractionated heparin 2.1%; enoxaparin 1.9%).

There were 8 hemorrhagic deaths reported during the trial. Hemorrhage was considered the primary cause of death in 6 patients: 3 in the heparin group (2 intracranial, 1 procedure related) and 3 in the enoxaparin group (1 intracranial, 2 procedure related). Hemorrhage was considered the secondary cause of death in 2 patients: 1 in the heparin group (procedure related) and 1 in the enoxaparin group (retroperitoneal).

## Discussion

The results of TIMI 11B indicate that for the acute management of unstable angina/non-Q-wave MI patients, enoxaparin is superior to unfractionated heparin for reducing a composite of death and serious cardiac ischemic events. This acute-phase superiority is achieved without a significant increase in the rate of either spontaneous or instrumented major hemorrhage. With respect to the outpatient phase, there was a durable treatment effect in that the initial treatment benefit with enoxaparin was sustained through day 43; however, no further relative decrease in events was observed. Although the absolute event rates were rather low, there was an increase in the rate of major hemorrhage (both spontaneous and instrumented) with outpatient enoxaparin treatment.

Despite receiving a weight-adjusted regimen, the patients assigned to the unfractionated heparin group in TIMI 11B had a similar therapeutic response to that treatment as seen in previous trials in which  $\approx 40\%$  to  $50\%$  of patients had an aPTT value in the target range while receiving unfractionated heparin infusions.<sup>20,22</sup> Although the protocol design led to a slightly longer median duration of treatment with enoxaparin (4.6 days) than with unfractionated heparin (3.0 days), it is unlikely that this difference in the duration of treatment played an important role in the observed benefit of enoxaparin, because a statistically significant treatment effect of enoxaparin was already evident at 48 hours (Figure 1). The benefits of enoxaparin were sustained in that relative risk reductions of  $\approx 15\%$  to  $20\%$  in primary end point events were observed through 43 days. Internal consistency across each element of the primary end point was also present. Although there was some quantitative variation in the magnitude of the treatment effect, the group assigned to enoxaparin experienced lower rates for each element at virtually all the time points analyzed in Table 2, which suggests that the composite end point was not driven primarily by 1 category of events. The trial was not powered to demonstrate significant differences in individual subgroups, but the vast majority of subgroups analyzed showed a trend in favor of enoxaparin, with larger treatment benefits seen in higher-risk subgroups, such as those with ECG changes or prior aspirin use. The acute-phase benefits of enoxaparin were not achieved at the

cost of a significant increase in the rate of major hemorrhage, although there was a significant increase in the rate of minor hemorrhage. The increase in minor hemorrhage was due largely to ecchymoses at the subcutaneous injection site and groin hematomas at sheath-insertion sites, 2 problems that are potentially modifiable by improvements in technique.

Given the lack of benefit of long-term administration of other low-molecular-weight heparins in patients with unstable angina/non-Q-wave MI, the outpatient-phase findings of TIMI 11B merit additional scrutiny. Whereas there was a progressive convergence of the event rates over time in trials comparing dalteparin with placebo, this was not observed with enoxaparin, as evidenced by a comparison of the ORs for the primary end point at days 8 and 43 in Table 2 (day 8=0.83, 95% CI 0.69 to 1.00 versus day 43=0.85, 95% CI 0.72 to 1.00). A potential explanation is that enoxaparin achieved a greater antithrombotic effect than dalteparin during the acute phase, with a reduced thrombus burden being carried forth to the chronic phase. In support of this hypothesis is the persistent separation of the Kaplan-Meier event curves for the 2 treatment groups in the ESSENCE trial at 1 year after enoxaparin therapy that was restricted to the acute phase.<sup>23</sup>

### Clinical Implications

The results of TIMI 11B suggest that for the acute phase of management of unstable angina/non-Q-wave MI, antithrombin therapy with enoxaparin is superior to unfractionated heparin. Because the median duration of acute treatment with enoxaparin in TIMI 11B was 4.6 days, it seems reasonable to continue its administration throughout the initial hospitalization. However, no incremental benefit appears to be achieved by continuing enoxaparin treatment beyond the initial hospitalization, and there is an increased risk of major hemorrhage in the outpatient setting.

Clinical perspective on the results of TIMI 11B can be gained by comparing it to those trials of glycoprotein IIb/IIIa receptor antagonists conducted in similar populations of patients.<sup>24–28</sup> Background antithrombin therapy in the glycoprotein IIb/IIIa receptor trials was intravenous unfractionated heparin, a logical choice because it was the standard treatment available at the time they were conducted; the new glycoprotein IIb/IIIa receptor antagonists were tested against placebo. In contrast, TIMI 11B and ESSENCE compared enoxaparin with the active control of intravenous unfractionated heparin.<sup>20</sup> When the data from TIMI 11B and ESSENCE were pooled in a meta-analysis, a stable 20% reduction in a composite of death and cardiac ischemic events was observed beginning at 48 hours and continuing through 43 day follow-up.<sup>29</sup>

Given the reduction in events reported with enoxaparin in TIMI 11B and ESSENCE, one may speculate that the reported quantitative benefits of the new glycoprotein IIb/IIIa receptor antagonists might have been modified if enoxaparin had been used as the antithrombin rather than unfractionated heparin, but the exact nature of its potential impact is unclear. Although it would be anticipated that the event rate would be lower in a control group receiving enoxaparin, thus tending to diminish the treatment effect of the glycoprotein IIb/IIIa

receptor antagonist, it is also possible that a combination of the powerful, multifaceted antithrombin effects of enoxaparin and antiplatelet effects of a glycoprotein IIb/IIIa receptor antagonist would be synergistic, leading to a marked reduction in events in the active-treatment group. These issues, plus the need for additional data on its optimal use during percutaneous coronary interventional procedures and adjunctive use with thrombolytic agents, are likely to frame future trials of enoxaparin therapy in acute coronary syndromes.

## Appendix

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### Acknowledgments

This work was supported by a grant from Rhône-Poulenc Rorer (Collegeville, Pa), the manufacturer of Lovenox (enoxaparin).

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