Enoxaparin as Adjunctive Antithrombin Therapy for ST-Elevation Myocardial Infarction

Results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 Trial

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**Background**—ENTIRE-TIMI 23 evaluated enoxaparin with full-dose tenecteplase (TNK) and half-dose TNK plus abciximab.

**Methods and Results**—Patients (n=483) with ST-elevation MI presenting <6 hours from symptom onset were randomized to full-dose TNK and either unfractionated heparin (UFH) (bolus 60 U/kg; infusion 12 U/kg per hour) or enoxaparin (1.0 mg/kg subcutaneously every 12 hours; initial 30 mg intravenous bolus), or half-dose TNK plus abciximab and either UFH (bolus 40 U/kg; infusion 7 U/kg per hour) or enoxaparin (0.3 to 0.75 mg/kg subcutaneously every 12 hours; initial intravenous bolus of 30 mg). With full-dose TNK and UFH, the rate of TIMI 3 flow at 60 minutes was 52% and was 48% to 51% with enoxaparin. Using combination therapy, the rate of TIMI 3 flow was 48% with UFH and 47% to 58% with enoxaparin. The rate of TIMI 3 flow among all UFH patients was 50% and was 51% among enoxaparin patients. Through 30 days, death/recurrent MI occurred in the full-dose TNK group in 15.9% of patients with UFH and 4.4% with enoxaparin (P=0.005). In the combination therapy group, the rates were 6.5% with UFH and 5.5% with enoxaparin. The rate of major hemorrhage with full-dose TNK was 2.4% with UFH and 1.9% with enoxaparin; with combination therapy, it was 5.2% using UFH and 8.5% with enoxaparin.

**Conclusions**—Enoxaparin is associated with similar TIMI 3 flow rates as UFH at an early time point while exhibiting advantages over UFH with respect to ischemic events through 30 days. These findings with enoxaparin are achieved with a similar risk of major hemorrhage. (*Circulation*. 2002;105:1642-1649.)

**Key Words:** fibrinolysis ■ myocardial infarction ■ heparin ■ anticoagulants

Pharmacological reperfusion regimens for ST-elevation myocardial infarction (STEMI) typically utilize a multimodality approach consisting of a fibrinolytic agent, antiplatelet agents, and an antithrombin agent. Important advances have occurred in the fibrinolytic component not only with the development of more fibrin-specific agents but also agents administered by bolus technique such as tenecteplase (TNK-TPA).1,2 Antiplatelet therapy includes aspirin and, with increasing frequency, intravenous glycoprotein IIb/IIIa inhibitors. Relatively little progress, however, has occurred in the antithrombin component in which unfractionated heparin (UFH) remains the standard.

Despite its widespread use, UFH has several deficiencies, whereas low molecular weight heparins (LMWH) offer the advantages of (1) a stable and predictable anticoagulant response to a given dose, eliminating the need for coagulation monitoring, (2) simpler administration via the subcutaneous route, and (3) greater inhibition of thrombin generation via a higher anti-Xa:IIa ratio.3 Additional pharmacological advantages include less sensitivity to the inhibitory effects of...
platelet factor 4, a greater capacity to release tissue factor pathway inhibitor, a lower propensity to promote activation and aggregation of platelets, and potential antiplatelet effects via higher degrees of suppression of von Willebrand factor.

Encouraging observations have been reported from Phase II trials with the LMWH enoxaparin as adjunctive therapy in patients with STEMI using both streptokinase and tPA. Based on its potential advantages over UFH and the promising findings cited above, we designed the ENTIRE-TIMI 23 trial to evaluate enoxaparin as adjunctive antithrombin therapy both with various forms of pharmacological reperfusion, including standard reperfusion using full-dose tenecteplase (TNK) and combination therapy with half-dose TNK plus abciximab.

**Methods**

The trial was conducted between February 2000 and September 2001 at 43 enrolling centers in Belgium, Canada, France, the Netherlands, Spain, and the United States. It was supported by the central units and core laboratories described in the Appendix.

**Eligibility Criteria**

Patients were eligible for inclusion if they were aged 21 to 75 years, had a qualifying episode of ischemic discomfort of at least 30 minutes duration within the prior 6 hours, and exhibited at least 0.1 mV ST-segment elevation in 2 limb leads or 0.2 mV ST-segment elevation in 2 contiguous precordial leads, as reported by the enrolling clinical center. Patients were excluded if they had any of the following findings. Cardiovascular: left bundle branch block, intraventricular conduction defect, or paced rhythm; MI or percutaneous coronary intervention within the prior 7 days; previous CABG surgery; cardogenic shock or pulmonary edema; Bleding Risks: a single reliable measurement of systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg at any time from initial medical contact to randomization; known prior history of stroke, transient ischemic attack, or central nervous system structural damage; active bleeding or history of hemorrhagic diathesis (within prior year); active peptic ulcer disease within 2 months, major surgery within prior 3 months; platelet disorder or thrombocytopenia, need for long-term anticoagulation therapy. Prior or Concomitant Therapy: treatment with abciximab within the prior 7 days or eptifibatide or tirofiban within the prior 24 hours, known allergy to aspirin or any study drug; treatment with an oral anticoagulant within the prior 5 days; thrombolytic therapy within the prior 7 days, or treatment with any LMWH or UFH within 24 hours prior to randomization. General: inability to undergo cardiac catheterization; MI precipitated by drugs other than aspirin or tPA. Patients were then randomized using a randomization ratios of either 1:2 or 1:3 were used (UFH:enoxaparin). The first measurement was 3 minutes after initiation of the reperfusion regimen (55 to 75 minutes duration within angiography if the systolic blood pressure was >110 mm Hg).

**Study Protocol**

In this open-label, dose-ranging study, all patients were given aspirin (≥160 mg PO or 250 to 500 mg IV followed by a daily maintenance dose of 100 to 325 mg PO). They were then randomized using a central telephone system as described below, stratifying for anterior or nonanterior location of the qualifying MI based on the presenting ECG (Figure 1).

Coronary angiography of the infarct-related artery was performed 60 minutes after admission. Enoxaparin dosing was stopped if the patient had a successful percutaneous intervention or was referred for bypass surgery. Enoxaparin regimens tested included those with and without an initial intravenous bolus of 30 mg, followed by dose ranging for the first 2 subcutaneous injections (spaced 12 hours apart), and then by a fixed dose of 1.0 mg/kg subcutaneously every 12 hours.

**Angiographic Procedures**

Time 0 was considered to be the time of administration of TNK. Coronary angiography of the infarct-related artery was performed 60 minutes after initiation of the reperfusion regimen (55 to 75 minutes). Investigators used standardized views and techniques of injection. The protocol specified that nitroglycerin (100 μg) either by intracoronary or intravenous route was to be administered every 15 minutes during angiography if the systolic blood pressure was >110 mm Hg.

**Clinical Procedures**

ECGs were obtained at admission, at 60 and 180 minutes after treatment, 48 hours after treatment, for any episodes of recurrent ischemic discomfort >10 minutes during the index hospitalization, and at hospital discharge. Creatine kinase (CK) and isoenzyme (CK-MB) levels were measured on admission and at 3 hours, and at
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6 to 8 hour intervals for the first 24 hours; these were repeated for episodes of recurrent ischemic discomfort or following revascularization procedures during the index hospitalization. Platelet counts were measured at admission, at 3, 24, and 48 hours following study drug, and again at hospital discharge.

All patients were followed for clinical events during the index hospitalization and through 30 days.

**Study End Points**

**Efficacy**

The primary angiographic efficacy end point was TIMI grade 3 flow at 60 minutes in the infarct related artery. All angiograms were evaluated by a single observer (C.M.G.) in the Angiographic Core Laboratory who was blinded to treatment assignment using previously established procedures for determination of TIMI flow grade and TIMI frame count. Patients were considered angiographically evaluable if they received the specified reperfusion regimen and had an evaluable 60 (55 to 75)-minute angiogram.

Three ECGs (admission, 60 [45 to 75] min, 180 [120 to 240] min) were quantitatively analyzed at the Core ECG Laboratory at the University of Leuven. ST-segment deviation (20 ms after the end of the QRS complex) was measured using a computer-assisted, custom-made in-house program. Two investigators performed measurements independently and were blinded to angiographic and clinical findings. ECGs were excluded for analysis for (1) left or right bundle branch block; (2) nonspecific intraventricular conduction delay; (3) left or right ventricular hypertrophy; and (4) pacing. ST-segment resolution was categorized as complete (>70%), partial (30 to 69%), or no resolution (<30%).

Clinical efficacy end points (all cause mortality, recurrent MI) were analyzed for all treated patients by a blinded Clinical Events Committee using standardized definitions. Criteria for reinfarction were as described previously.10,11 The composite end point death/nonfatal recurrent MI (death/MI) was analyzed through 30 days.

**Safety**

The primary safety end point was TIMI major hemorrhage at 30 days, defined as any clinically overt hemorrhage associated with a drop in hemoglobin ≥5 g/dL (not associated with CABG) or intracranial hemorrhage or cardiac tamponade.12,13 All patients receiving any element of the assigned reperfusion regimen were included in safety analyses (treated cohort). Hemorrhages were also reviewed and classified by the Clinical Events Committee.

**Statistical Considerations**

To guide the Operations Committee in evaluating doses of enoxaparin, a sequential probability ratio test (SPRT) was used as previously described. For the standard reperfusion groups, the lower (H₀) and upper (Hₐ) boundaries were TIMI 3 flow rates at 60 minutes of 35% and 60%. The H₀ and Hₐ boundaries for the combination reperfusion groups were 55% and 80%, respectively. The α and β errors were set at 1%. Based on the operating characteristics of the SPRT, it was estimated that 35 to 70 patients per treatment group would provide sufficient information to determine whether a given regimen was likely to be considered a candidate for additional testing.

Statistical comparisons between enoxaparin and UFH, either pooling the enoxaparin regimens within each form of pharmacological reperfusion or collapsing all groups of each antithrombin across pharmacological reperfusion strategies, were performed by the Wald χ² test (logistic regression) adjusted for MI location (anterior/nonanterior). Because of the exploratory nature of the comparisons in the trial, nominal probability values without adjustment for multiple comparisons were taken as an indicator of the statistical significance of comparisons between groups or trends among groups.

**Results**

A total of 488 patients were enrolled in the trial. Of these, 483 (99%) were treated. 242 received full-dose TNK (82 UFH, 160 enoxaparin), and 241 received half-dose TNK plus abciximab (77 UFH, 164 enoxaparin). Therefore, 159 patients were treated with one of the 2 UFH control regimens while 324 were treated with one of 5 enoxaparin regimens. No important differences in baseline characteristics were observed among the patients in the 7 different regimens studied. A composite list of characteristics is therefore shown in Table 1. The median time from the onset of pain to administration of TNK was 3.0 hours. The time from randomization to TNK

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Standard Reperfusion</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients</td>
<td>UFH</td>
</tr>
<tr>
<td><strong>No. patients</strong></td>
<td>483</td>
<td>82</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>58 (51, 66)</td>
<td>56 (50, 66)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>398 (82)</td>
<td>69 (84)</td>
</tr>
<tr>
<td>Female</td>
<td>85 (18)</td>
<td>13 (16)</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>81 (72, 90)</td>
<td>81 (74, 90)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>65 (14)</td>
<td>13 (16)</td>
</tr>
<tr>
<td><strong>Hx hypertension</strong></td>
<td>125 (26)</td>
<td>18 (22)</td>
</tr>
<tr>
<td><strong>Current smoker</strong></td>
<td>257 (53)</td>
<td>47 (57)</td>
</tr>
<tr>
<td><strong>Prior MI</strong></td>
<td>53 (11)</td>
<td>3 (4)</td>
</tr>
<tr>
<td><strong>Prior PCI</strong></td>
<td>32 (7)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Location of MI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>170 (35)</td>
<td>32 (39)</td>
</tr>
<tr>
<td>Nonanterior</td>
<td>313 (65)</td>
<td>50 (61)</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>137 (120, 150)</td>
<td>140 (126, 155)</td>
</tr>
<tr>
<td><strong>Time</strong></td>
<td>3.0 (2.1, 3.9)</td>
<td>3.0 (2.1, 4.0)</td>
</tr>
</tbody>
</table>

Data are shown as n (%) for dichotomous variables and median (25, 75th percentile) for continuous variables.
### TABLE 2. Angiographic Observations

<table>
<thead>
<tr>
<th></th>
<th>Standard Reperefusion</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TNK (0.53 mg/kg)</td>
<td>TNK (0.27 mg/kg) + Abciximab (bolus 0.25 mg/kg, infusion 0.125 µg/kg per minute for 12 hours)</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolus, U/kg</td>
<td>60 (max 4000)</td>
<td>40 (max 3000)</td>
</tr>
<tr>
<td>Infusion, U/kg/hour</td>
<td>12 (max 1000)</td>
<td>7 (max 800)</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolus, mg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Initial sc injections, mg/kg</td>
<td>1.0 (max 100 mg)</td>
<td>- 0.3 (max 100 mg)</td>
</tr>
<tr>
<td>Maintenance sc injections, mg/kg</td>
<td>1.0 1.0</td>
<td>1.0 1.0 1.0</td>
</tr>
<tr>
<td>No. patients treated</td>
<td>82 81 79</td>
<td>60 77 48 77 39 154</td>
</tr>
<tr>
<td>TIMI 3</td>
<td>38 (52) 36 (51)</td>
<td>34 (65) 70 (50)</td>
</tr>
<tr>
<td>TIMI 2</td>
<td>20 (27) 17 (24)</td>
<td>21 (30) 38 (27)</td>
</tr>
<tr>
<td>TIMI 25</td>
<td>58 (60) 53 (76)</td>
<td>55 (76) 108 (77)</td>
</tr>
<tr>
<td>CTFC</td>
<td>42 (33,74) 40 (28,100) 941 (27,100)</td>
<td>40 (27,100) 36 (27,100) 943 (24,100) 45 (29,100) 40 (29,100)</td>
</tr>
<tr>
<td>Angio Eval Pts at 60 min</td>
<td>73 70 71</td>
<td>67 36 68 33 134</td>
</tr>
<tr>
<td>Antithrombin therapy for PCI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target ACT</td>
<td>250 sec</td>
<td>200 sec</td>
</tr>
<tr>
<td>Intravenous bolus</td>
<td>≤5000 U</td>
<td>None</td>
</tr>
<tr>
<td>Saphenous removal</td>
<td>4 hours after PCI</td>
<td>4 hours after PCI</td>
</tr>
</tbody>
</table>

Angio Eval Pts indicates angiographically evaluable patients; cTFC, corrected TIMI frame count; sc, subcutaneous; TNK, tenecteplase; UFH, unfractionated heparin; and N/A, not applicable.

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

### TABLE 3. Electrocardiographic Observations

<table>
<thead>
<tr>
<th></th>
<th>Standard Reperefusion</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TNK (0.53 mg/kg)</td>
<td>TNK (0.27 mg/kg) + Abciximab (bolus 0.25 mg/kg, infusion 0.125 µg/kg per minute for 12 hours)</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolus, U/kg</td>
<td>60 (max 4000)</td>
<td>40 (max 3000)</td>
</tr>
<tr>
<td>Infusion, U/kg/hour</td>
<td>12 (max 1000)</td>
<td>7 (max 800)</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolus, mg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Initial sc injections, mg/kg</td>
<td>1.0 (max 100 mg)</td>
<td>- 0.3 (max 100 mg)</td>
</tr>
<tr>
<td>Maintenance sc injections, mg/kg</td>
<td>1.0 1.0</td>
<td>1.0 1.0 1.0</td>
</tr>
<tr>
<td>No. patients treated</td>
<td>82 81 79</td>
<td>60 77 48 77 39 154</td>
</tr>
<tr>
<td>ECG Eval Pts at 90 min*</td>
<td>41 50 40</td>
<td>37 26 34 22 76</td>
</tr>
<tr>
<td>Complete ST resolution</td>
<td>9 (20) 9 (18)</td>
<td>9 (24) 2 (10) 6 (18) 5 (23) 13 (17)</td>
</tr>
<tr>
<td>ECG Eval Pts at 180 min*</td>
<td>55 58 56</td>
<td>54 35 54 27 116</td>
</tr>
<tr>
<td>Complete ST resolution</td>
<td>21 (38) 27 (49)</td>
<td>26 (52) 18 (51) 31 (57) 15 (56) 64 (55)</td>
</tr>
</tbody>
</table>

ECG Eval Pts indicates ECG-gradable patients; sc, subcutaneous; TNK, tenecteplase; and UFH, unfractionated heparin.

Data are shown as n (%) for evaluable patients) for dichotomous variables.

*The proportion of patients considered nongradable because of lack of performance of an ECG, a tracing performed outside the time window, or a technically inadequate tracing at baseline or followup were 3.3%, 20.5%, and 25.7% at 60 min and 3.7%, 6.4%, and 20.1% at 180 min. There was a statistically significant trend toward an increased proportion of patients exhibiting complete ST resolution at 180 min progressing from standard reperfusion (38% with UFH, 47% with enoxaparin) to combination therapy (52% with UFH, 55% with enoxaparin), P<0.04 by x2 for linear trend. None of the individual comparisons between UFH and enoxaparin was significant.
was a median of 21 (16, 26) minutes in the full-dose TNK group and was slightly longer at 30 (22, 37) minutes in the half-dose TNK plus abciximab group.

The median duration of therapy in the group assigned to UFH was 44 (26, 65) hours and by protocol design was longer in the enoxaparin group at 76 (32, 156) hours. During the first 6 hours after receiving the reperfusion regimen, patients treated with UFH had a median aPTT value 2 (1.5, 3.3) times control in the full-dose TNK group whereas those treated with half-dose TNK plus abciximab had median values 1.2 (1.0, 2.0) times control.

The dose regimens for UFH and enoxaparin therapy are summarized in Table 2.

Angiographic Observations
Of the 483 treated patients, 415 (86%) had an evaluable angiogram at 60 minutes. Reasons for exclusion from the angiographically evaluable cohort at 60 minutes were lack of angiography for clinical reasons (n = 110056 [1.2%]) or performance of the angiogram outside the 60-minute timeframe (n = 110055 [11%]) and technically inadequate imaging (n = 110057 [1.4%]).

With full-dose TNK, the rate of TIMI 3 flow in the UFH group was 52% and was 48% to 51% in the enoxaparin groups (Table 2). With combination therapy, the rate of TIMI 3 flow was 48% in the UFH group and 47% to 58% in the enoxaparin groups. Collapsing across both forms of pharmacological reperfusion (full-dose TNK and combination therapy), the pooled rate of TIMI 3 flow was 50% in patients receiving UFH and 51% to 57% in the enoxaparin groups. The pooled rate of complete ST-resolution was 52% in the UFH group and 51% to 57% in the enoxaparin groups. The pooled rate of complete ST-resolution at 180 minutes was 45% in patients receiving UFH and 51% in patients receiving enoxaparin (Table 3).

Electrocardiographic Observations
Of the 483 patients, 244 (51%) had an evaluable ECG at 60 minutes (see Table 3 for details). The proportion of patients receiving full-dose TNK who exhibited complete ST-resolution at 60 minutes was 20% in the UFH group and 18% to 20% in the enoxaparin groups (Table 3). The rate of complete ST-resolution in the patients receiving combination therapy was 24% in the UFH group and 10% to 23% in the enoxaparin groups. The pooled rate of complete ST-resolution at 60 minutes was 22% in patients receiving UFH and 18% in patients receiving enoxaparin (Table 3).

Of the 483 patients, 337 (70%) had an evaluable ECG at 180 minutes (see Table 3). The proportion of patients exhibiting complete ST-resolution at 180 minutes with full-dose TNK was 38% in the UFH group and 46% to 48% in the enoxaparin groups (Table 3). Among patients receiving combination therapy, the rate of complete ST-resolution was 52% in the UFH group and 51% to 57% in the enoxaparin groups. The pooled rate of complete ST-resolution at 180 minutes was 45% in patients receiving UFH and 51% in patients receiving enoxaparin (Table 3).

To remove the potential confounding effect of PCI on ST-resolution at 180 minutes, the subset of 225 evaluable patients who did not undergo a PCI between 60 and 180 minutes was analyzed. The pooled rate of complete ST-resolution at 180 minutes with full-dose TNK was 38% in the UFH group and 41% to 46% in the enoxaparin groups. With combination therapy, the rate of complete ST-resolution was 50% in the UFH group and 55% to 58% in the enoxaparin groups. The pooled rate of complete ST-resolution at 180 minutes was 43% in patients receiving UFH and 50% in those receiving enoxaparin.

Clinical Events
Through 30 days, the composite end point of death/MI in patients in the full-dose TNK group was 15.9% with UFH and 4.4% with enoxaparin (P = 0.005) (Figure 2). This was mediated largely by a reduction in the rate of nonfatal reinfarction: 12.2% with UFH and 1.9% with enoxaparin (P = 0.003). In the combination therapy group, death/MI occurred in 6.5% of UFH patients and 5.5% of enoxaparin patients. The pooled rate among all UFH patients was 11.3% and was 4.9% in enoxaparin patients (P = 0.01) (Figure 3).

The incidence of MI was analyzed stratified by whether a PCI was performed through 30 days. Among the 259 patients...
Death/MI (D30) 
Time to Events

Figure 3. Kaplan-Meier curves for death/myocardial infarction (MI). The rate of death/MI was highest in the group receiving full-dose TNK and UFH (6.1% at 36 hours) with events continuing to occur throughout the first 30 days (15.9%). Patients treated with full-dose TNK and enoxaparin had a lower rate of death/MI both during the period of head-to-head comparison with UFH (1.3% at 36 hours; \( P = 0.066 \)) and during the course of the first 30 days (4.4%; \( P = 0.005 \) by chi square test and \( P = 0.003 \) by log rank test). Patients treated with combination therapy had similar rates of death/MI with UFH and enoxaparin (\( P = 0.67 \)).

who did not undergo PCI, recurrent MI occurred in 6 (7.6%) of patients treated with UFH and 2 (1.1%) patients treated with enoxaparin. A PCI was performed in 224 (46%) patients. Among the 80 UFH-treated patients undergoing PCI, recurrent MI occurred in 6 (7.5%) prior to the procedure and in 1 (1.3%) after the procedure. Among the 144 enoxaparin-treated patients undergoing PCI, a recurrent MI occurred in 2 (1.4%) prior to the procedure and in 2 (1.4%) after the procedure.

Through 30 days, the overall rate of TIMI major hemorrhage was 4.8%. Because no important differences were observed among the enoxaparin regimens, the data were pooled for comparison with UFH. Among patients receiving full-dose TNK, the rate of major hemorrhage with UFH was 2.4% and was 1.9% with enoxaparin (Figure 4). The rates of major hemorrhage were higher with combination therapy: 5.2% with UFH and 8.5% with enoxaparin. The pooled rate of major hemorrhage was 3.8% in patients receiving UFH and 5.2% in patients receiving enoxaparin.

Of the 224 patients who underwent PCI, 13 (5.8%) experienced a major hemorrhage that was at an instrumented site in 10 patients. When PCI was performed in patients who had been assigned to full-dose TNK, the rate of major hemorrhage with UFH was 4.9% and was 1.8% with enoxaparin. When PCI was performed in patients assigned to combination therapy, the rates of major hemorrhage were 7.7% with UFH and 8.0% with enoxaparin. Collapsing across both forms of pharmacological reperfusion, the rate of major hemorrhage in the PCI cohort was 6.3% in patients receiving UFH and 5.6% in patients receiving enoxaparin.

Discussion
The results of the ENTIRE-TIMI 23 trial suggest that enoxaparin is associated with similar TIMI 3 flow rates as UFH at an early time point after administration of the bolus fibrinolytic TNK, while exhibiting advantages over UFH with respect to ischemic events through 30 days. This constellation of findings with enoxaparin appears to be achieved at a similar risk of major hemorrhage. Our pilot observations in ENTIRE-TIMI 23 are consistent with proposed advantages of enoxaparin over UFH and are concordant with the results of other trials of enoxaparin in STEMI.4,5,14

When compared with full-dose TNK, combination therapy with half-dose TNK plus abciximab was associated with a similar TIMI 3 flow rate at 60 minutes and a trend toward more complete ST-segment resolution at 180 minutes regardless of the antithrombin administered. Although the number of patients studied was small, the reduction in the rate of recurrent MI and the increase in major hemorrhage observed with combination therapy in this trial was consistent with observations in Global Utilization of Streptokinase and tPA for Occluded Arteries (GUSTO)-V13 and Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT)-3,13

The balance of fibrinolytic activity and procoagulant activity plays an important role in the effectiveness of a pharmacological reperfusion regimen for STEMI. Following fibrinolytic therapy, the coagulation cascade may be stimulated as a consequence of exposure of clot-bound thrombin. Increased local concentrations of thrombin amplify the formation of fibrin thrombi and also lead to activation of platelets. Considerations such as these are fundamental to the ongoing practice of prescribing antithrombin therapy along with a fibrinolytic agent (of the direct plasminogen activator type) and aspirin for STEMI. Angiographic studies suggest that although adjunctive therapy with UFH may not improve the likelihood of achieving patency (TIMI 2+3 flow) of the infarct related artery at an early time point (90 minutes),16 it does appear to prevent reocclusion and help maintain patency of the infarct artery when assessed at later time points such as 18 to 96 hours.17-19

A major deficiency of UFH is its limited ability to inhibit the generation of thrombin, resulting in rebound activation of the coagulation cascade following cessation of an infusion.3 Evidence exists from prior trials suggesting that during the period of its administration, use of UFH is associated with a lower mortality compared with placebo.20,21 Enoxaparin, with an anti-Xa:IIa ratio of 3.8:1 provides greater inhibition of more proximal reactions in the coagulation cascade. This property of enoxaparin coupled with its stable anticoagulant effect and convenient method of administration led to our

![TIMI Major Hemorrhage (30d)](image_url)

Figure 4. Rate of TIMI major hemorrhage through 30 days for various treatment groups. ICH indicates intracranial hemorrhage.
testing of a strategy of early adjunctive therapy with enoxaparin at the time of fibrinolysis and continued through the index hospitalization.

The nearly identical rates of TIMI 3 and TIMI 2+3 flow at 60 minutes observed with enoxaparin and UFH are reassuring. We speculate that a combination of greater inhibition of thrombin generation, more stable anticoagulant effect, and more protracted course of treatment with enoxaparin lead to a reduced thrombus burden in the epicardial infarct artery and subserved myocardial microvasculature as well as less platelet activation. These actions may have translated into fewer patients experiencing death or recurrent MI. The similar rates of major hemorrhage with enoxaparin are encouraging in light of the longer duration of treatment with enoxaparin than UFH. The safety observations from ENTIRE-TIMI 23 suggest that there appears to be no increase in risk of major bleeding with enoxaparin compared with UFH when standard reperfusion is used.

Our study did not definitively identify a dose of enoxaparin that clearly emerged as the most attractive regimen with respect to efficacy or safety. Arguments in favor of an initial intravenous bolus are the more reliable delivery of enoxaparin (because in some patients, perfusion of subcutaneous tissues may be compromised in the first few hours after MI) and the fact that anti-Xa levels are predicted to be ≥0.6 IU/mL by pharmacokinetic modeling, a range where PCI can be performed.22,23 The regimen proposed for standard reperfusion (30 mg IV bolus and 1.0 mg/kg subcutaneous injections every 12 hours) has also undergone testing in the Low Dose Enoxaparin in Acute MI (GUSTO-V15) study. The development of a subcutaneous dose of enoxaparin during the first day proposed for combination therapy utilizes a bolus and a reduced subcutaneous dose of enoxaparin during the first day (0.3 mg/kg subcutaneously every 12 hours) by analogy to the recommendation of reducing the dose of UFH for patients receiving combination reperfusion as tested in GUSTO-V13 and ASSENT-3.14

The findings of ENTIRE-TIMI 23, when coupled with the results of ASSENT-3, suggest that phase III trials are now needed to evaluate enoxaparin as a replacement for UFH in a variety of pharmacological reperfusion regimens including different lytics in full-dose and as part of combination therapy regimens with different glycoprotein IIb/IIIa inhibitors. The convenient mode of administration and lack of need for anticoagulation monitoring with enoxaparin also make it an attractive agent for testing as part of a prehospital treatment strategy for STEMI as is being explored in the ASSENT-3 plus study.

Appendix

ENTIRE-TIMI 23 Participants

A full list of participants can be found in the online-only Data Supplement.

Study Coordination

TIMI Study Chairman’s Office: Harvard Medical School, Brigham and Women’s Hospital, Boston, Mass. Eugene Braunwald, MD; North America Study Chairman: Elliott M. Antman, MD; Project Director: Sally Cutler. Leuven Coordinating Center, Leuven, Belgium. European Study Chairman: Frans Van de Werf, MD, PhD. Sponsor: Aventis Pharma, Antony, France. Project Leader: Frédérique Bigonzi, MD; Study Leader: Ghislaine Pisapia. Angiographic Core Laboratory: PERFUSE, Harvard Clinical Research Institute, Boston, Mass. Principal Investigator: C. Michael Gibson, MD, MS. ECG Core Laboratory: Leuven Coordinating Center, Leuven, Belgium. Director: Hein Heidbuchel, MD, PhD. CEC: Leuven Coordinating Center, Leuven, Belgium: Peter Sinaeve, MD, Chairman.

Data Management and Statistics, Aventis Pharma: Stéphane Pave- ageau; Véronique Le-Louer; Carole Heccquet. Operations Committee: Elliott M. Antman, MD; Frans Van de Werf, MD, PhD; Frédérique Bigonzi, MD; Véronique Le-Louer.

Enrollment by Country: Lead Investigators

Netherlands (261 patients) G.P. Molhoek, MD, WCN; Spain (71 patients) J.L. Lopez-Sendon, MD; Belgium (54 patients) F. Van de Werf, MD, PhD; France (45 patients) J.-P. Bassand, MD; United States (45 patients) E.M. Antman, MD; Canada (12 patients).

Acknowledgments

The work was supported by a grant from AVENTIS Pharma, 20 Avenue R. Aron, 92105 Antony, France. Genentech provided TNK-tPA (tenecteplase).

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Enoxaparin as Adjunctive Antithrombin Therapy for ST-Elevation Myocardial Infarction: Results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 Trial

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for the ENTIRE-TIMI 23 Investigators

Circulation. 2002;105:1642-1649; originally published online March 4, 2002; doi: 10.1161/01.CIR.0000013402.34759.46

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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