Randomized Evaluation of the Safety and Efficacy of Enoxaparin Versus Unfractionated Heparin in High-Risk Patients With Non–ST-Segment Elevation Acute Coronary Syndromes Receiving the Glycoprotein IIb/IIIa Inhibitor Eptifibatide

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Background—Current pharmacotherapeutic options for high-risk non–ST-segment elevation acute coronary syndrome patients include aspirin, clopidogrel, heparin, and platelet glycoprotein IIb/IIIa inhibition. A key issue of uncertainty is the safety and efficacy of combination glycoprotein IIb/IIIa inhibitor and low-molecular-weight heparin therapy.

Methods and Results—We randomized 746 patients with rest ischemic discomfort within 24 hours after the onset of symptoms and ST-segment deviation and/or elevation of serum cardiac markers to receive open-label enoxaparin (1 mg/kg subcutaneously twice daily) or unfractionated heparin (70-U/kg bolus; 15 U · kg\(^{-1}\) · h\(^{-1}\) infusion, titrated to an activated partial thromboplastin time of 1.5 to 2 times control) for 48 hours. All patients received aspirin and eptifibatide (180-mg/kg bolus; 2 mg · kg\(^{-1}\) · min\(^{-1}\) infusion). Major non–coronary artery bypass surgery–related bleeding at 96 hours (primary safety outcome) was significantly lower among enoxaparin-treated patients than among heparin-treated patients (1.8% versus 4.6%, \(P=0.03\)). Minor bleeding was more frequent in the enoxaparin group (30.3% versus 20.8%, \(P=0.003\)). Patients in the enoxaparin group were less likely to experience ischemia as detected by continuous ECG evaluation (primary efficacy outcome) during the initial (14.3% versus 25.4%, \(P=0.0002\)) and subsequent (12.7% versus 25.9%, \(P<0.0001\)) 48-hour monitoring periods. Death or myocardial infarction at 30 days was significantly lower in the enoxaparin group (5% versus 9%, \(P=0.031\)).

Conclusions—When aspirin and eptifibatide are used in high-risk non–ST-segment elevation acute coronary syndrome patients, enoxaparin improves outcomes (determined on the basis of better safety and efficacy) compared with currently recommended unfractionated heparin therapy and provides a useful novel alternative therapeutic strategy. (Circulation. 2003;107:r8-r14.)

Key Words: myocardial infarction ■ angina, unstable ■ heparin ■ anticoagulants

Current pharmacotherapeutic options for patients with high-risk non–ST-segment elevation acute coronary syndromes (ACS) include aspirin, clopidogrel, heparin, and platelet glycoprotein IIb/IIIa inhibition. Although the low-molecular-weight heparin (LMWH) enoxaparin has been demonstrated to be superior to unfractionated heparin (UFH) in two trials, these did not include concomitant therapy with glycoprotein IIb/IIIa antagonists. Hence, a key remaining issue is the safety and efficacy of combination glycoprotein IIb/IIIa inhibitor and LMWH therapy. We hypothesized that the rates of major hemorrhage would be equivalent and rates of ischemia lower in glycoprotein IIb/IIIa inhibitor–treated patients receiving enoxaparin versus UFH.

Methods

Study Patients
Patients were eligible if they were ≥18 years of age and hospitalized with ischemic chest discomfort of ≥10 minutes’ duration occurring at rest and ≤24 hours before enrollment. In addition, patients were required to have: (1) ST-segment depression ≥0.1 mV or transient
ST-segment elevation $\geq 0.1$ mV in $\geq 2$ contiguous ECG leads; and/or (2) elevation (determined by the local laboratory) of troponin I or T $\geq 3$ times the upper reference limit, or creatine kinase (CK)-MB higher than normal.

Patients were excluded if they had any of the following findings: (1) Cardiovascular: uninterpretable ST segment based on baseline 12-lead ECG (eg, left bundle-branch block); ischemia due to an established precipitating cause (eg, heart failure); cardiogenic shock; or scheduled or recent revascularization (coronary artery bypass surgery in previous 2 months or percutaneous coronary intervention [PCI] in previous 6 months). (2) Bleeding risk: blood pressure $>200$ mm Hg systolic or $>110$ mm Hg diastolic; hemoglobin $<11$ g/dL for men or $9$ g/dL for women; thrombocytopenia; ulcerative gastrointestinal disease in previous 6 months; history of cerebral hemorrhage or known intracerebral vascular disease; nonhemorrhagic stroke in previous month; eye, spinal, or central nervous system surgery in previous 2 months; major surgery, organ biopsy, puncture of noncompressible vessel in previous 2 weeks; or known or suspected pregnancy. (3) Prior or concomitant therapy: treatment with abciximab in previous 14 days or with tirofiban or epifibatide in previous 7 days; allergy or contraindication to aspirin or study drugs; oral anticoagulation treatment in previous 5 days or INR $>1.2$; fibrinolysis in previous 24 hours; or treatment with investigational agents in previous 30 days. (4) General: renal failure (estimated creatinine clearance <30 mL/min or creatinine $>2$ mg/dL) or other serious disease, including liver failure; or inability to commence ST-segment monitoring $\leq 8$ hours after randomization.

Initially, patients were also excluded if they had received UFH or LMWH $\leq 24$ hours before enrollment. However, after 265 patients had been enrolled, the independent data and safety monitoring board (independent of the investigator) amended the protocol that included patients who had received UFH or enoxaparin $\leq 12$ hours before enrollment.

**Study Medications**

After they had given written informed consent, patients were treated with epifibatide (Schering Canada Inc): $180$-mg/kg bolus followed by a $2.0$-$\mu$g $\cdot$ kg$^{-1} \cdot$ min$^{-1}$ infusion for 48 hours. All patients received oral aspirin in a dose of $\geq 160$ mg initially, followed by $80$ to $325$ mg daily. On the basis of a computer-generated randomization code, with stratification according to center, a sequential, sealed envelope was opened at the enrolling site and patients were randomized to receive either enoxaparin (Aventis Canada; $1$ mg/kg of body weight [100 anti-factor Xa units/kg] subcutaneously every 12 hours for 48 hours) or UFH ($70$-U/kg intravenous bolus followed by a $15$-U $\cdot$ kg$^{-1} \cdot$ h$^{-1}$ continuous infusion, titrated to an activated partial-thromboplastin time [aPTT] of $1.5$ to $2$ times control for 48 hours).

Use of any other medications, the decision to proceed with angiography, and the use of revascularization were left to the discretion of the investigator.

**Study Organization**

Patients were recruited between September 1, 2000, and December 21, 2001, at 50 centers in Canada. The ethics review board at each institution approved the study. The study was conceived, designed, coordinated, and all the data managed and analyzed, by the Canadian Heart Research Center. The steering committee oversaw the study and the data were periodically reviewed by an independent data and safety monitoring board.

**Outcome Measures**

The primary safety outcome was the incidence of 96-hour, non–coronary artery bypass surgery (CABG)–related major bleeding. Major bleeding included bleeding resulting in death, or retroperitoneal hemorrhage, or bleeding at a specific site accompanied by a drop in hemoglobin $\geq 3$ g/dL. Minor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding.

The primary efficacy outcome was assessed by the rate of recurrent ischemia detected during continuous ECG monitoring. Seven-lead, three-channel ST-segment monitoring (Applied Cardiac Systems) was performed for 96 hours after randomization. Evaluation within the first 48 hours and in the >48- to 96-hour window was prespecified and based on the hypothesis that treatment differences would be evident both during study drug administration and after study drug discontinuation. Analysis was performed initially by use of an automated algorithm and subsequently reviewed twice by a cardiologist blinded to the clinical data and treatment assignment. Significant ST-segment shift was defined as horizontal or downsloping ST depression $\geq 0.1$ mV below the baseline or upward ST elevation $\geq 0.1$ mV above the baseline, lasting $\geq 1$ minute in duration, and separated from other episodes of ST-segment shift by $\geq 1$ minute.

Secondary clinical outcomes were prespecified and included the composite of 30-day (1) death or nonfatal myocardial (re)infarction (MI), or (2) death, MI, or recurrent angina (with ECG changes and/or urgent revascularization). MI was considered postenrollment if CK-MB was above the upper limit of normal (ULN), increased by $\geq 50\%$ over the previous value, and not elevated $\leq 16$ hours before enrollment; if the troponin T or I was $>3$ times the upper reference limit and not elevated $\leq 12$ hours before enrollment; or if $\leq 24$ hours after coronary revascularization, the CK-MB was $>3$ times (PCI) or 5 times (CABG) the ULN and increased by $\geq 50\%$ of the previous value. Recurrent angina with ECG changes was defined as symptoms of ischemia with new ECG changes detected on 12-lead ECG despite the use of nitrates and either $\beta$-blockers or calcium-channel blockers. Recurrent angina requiring urgent revascularization was defined as symptoms of ischemia, either during the index hospitalization or resulting in rehospitalization, that prompted coronary revascularization.

### TABLE 1. Baseline Characteristics, Medical History, Electrocardiographic Changes, and Cardiac Marker Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Epifibatide and Enoxaparin (n=380)</th>
<th>Epifibatide and UFH (n=366)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age,* y</td>
<td>64 (54, 72)</td>
<td>64 (54, 73)</td>
</tr>
<tr>
<td>Female sex</td>
<td>121 (31.8)</td>
<td>112 (30.6)</td>
</tr>
<tr>
<td>Time from onset of symptoms to randomization,* h</td>
<td>4.4 (2.8, 7.7)</td>
<td>4.4 (2.8, 6.7)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>110 (29.0)</td>
<td>103 (28.1)</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>36 (9.5)</td>
<td>41 (11.2)</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>39 (10.3)</td>
<td>31 (8.5)</td>
</tr>
<tr>
<td>Prior stroke/transient ischemic attack</td>
<td>24 (6.3)</td>
<td>29 (7.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>186 (49.0)</td>
<td>178 (48.6)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>171 (45.0)</td>
<td>163 (44.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>105 (27.6)</td>
<td>111 (30.3)</td>
</tr>
<tr>
<td>Heart rate,* bpm</td>
<td>70 (61, 81)</td>
<td>72 (63, 82)</td>
</tr>
<tr>
<td>Systolic blood pressure,* mm Hg</td>
<td>134 (120, 150)</td>
<td>134 (120, 151)</td>
</tr>
<tr>
<td>Diastolic blood pressure,* mm Hg</td>
<td>77 (66, 87)</td>
<td>77 (68, 87)</td>
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<td>Killip class</td>
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<tr>
<td>I</td>
<td>340 (89.7)</td>
<td>321 (88.0)</td>
</tr>
<tr>
<td>II to IV</td>
<td>39 (10.3)</td>
<td>44 (12.0)</td>
</tr>
<tr>
<td>Transient ST elevation</td>
<td>24 (6.4)</td>
<td>24 (6.7)</td>
</tr>
<tr>
<td>ST depression</td>
<td>63 (16.8)</td>
<td>54 (15.0)</td>
</tr>
<tr>
<td>CK-MB and/or troponin elevation</td>
<td>311 (81.8)</td>
<td>312 (85.3)</td>
</tr>
</tbody>
</table>

Data are shown as n (%).
Safety and efficacy outcomes were adjudicated independently on two separate occasions by a cardiologist who was blinded to treatment assignment, and included review of all laboratory tests (regardless of whether an end point was identified by the site investigator), ECGs, and reports of bleeding and ischemia.

Statistical Analysis

Safety
This was a noninferior safety comparison between the two treatment groups, designed to show that the 96-hour incidence of major hemorrhage after eptifibatide and enoxaparin did not exceed by >2% that after eptifibatide and UFH therapy. The estimated sample size of 720 patients was determined with a one-sided 95% confidence interval for the difference between the two treatments, assuming an equal major bleeding rate of 2% and an upper limit of 4% for the confidence interval.

Efficacy
This was a superiority efficacy comparison between the two treatment groups consistent with our previous finding5 and was designed to show that treatment with enoxaparin would reduce the incidence of ischemia monitored during the initial 48- and 48- to 96-hour periods of continuous electrocardiographic monitoring from 30% to 21% with a power ranging from 69% to 74% (with an estimated nonevaluable/dropout rate ranging from 10% to 20%; 2-sided $\chi^2$ test, $\alpha=0.05$).

All safety and efficacy analyses were based on the intention-to-treat principle and used either the log-rank or $\chi^2$ statistic. Follow-up to 30 days was complete in all patients.

Results
The baseline characteristics, medical history, ECG changes, and drug therapies of the patients were similarly distributed in the two treatment groups and are shown in Table 1. Treatments and procedures are listed in Table 2.
5.5%; \( P = 0.016 \) and at 30 days (5.3% versus 8.7%; \( P = 0.062 \)). There were no intracranial hemorrhages. Rates of major bleeding among patients undergoing PCI (1 of 20 versus 5 of 57 patients, \( P = 1.0 \)) and CABG (1 of 1 versus 6 of 7 patients, \( P = 1.0 \)) within 12 hours of receiving enoxaparin or UFH were similar. Transfusion rates were similar in the two treatment groups, including those who underwent CABG (Table 3). There were no major CABG-related bleeds that required surgical reexploration.

Minor bleeding was more frequent in the enoxaparin than in the UFH group at 96 hours (30.3% versus 20.8%; \( P = 0.003 \)) (Table 3). The higher rate of 96-hour minor bleeding mainly was due to more local skin injection site ecchymoses (8.9% versus 4.1%; \( P = 0.01 \)) and oropharyngeal bleeding (predominantly epistaxis; 15.8% versus 11.2%; \( P = 0.07 \)).

Within the first 12 hours, only 16.7% of patients receiving UFH had an aPTT within the therapeutic range (1.5 to 2 times control); 69% were above the therapeutic range (>2 times control) and the median aPTT was 97 (25th, 75th percentiles: 61, 48) seconds. By 24 hours, 46.7% of UFH patients were in the therapeutic range; the median aPTT was 67 (54, 90) seconds.

**Continuous ECG Monitoring**

Patients receiving eptifibatide and enoxaparin compared with eptifibatide and UFH had lower rates of ischemia during the first 48 hours (14.3% versus 25.4%; \( P = 0.0002 \)) and subsequent 48 hours (12.7% versus 25.9%; \( P < 0.0001 \)) (Figure 1). Regardless of treatment, patients experiencing ST-segment shift compared with those without ST shift during continuous monitoring had a significantly higher 30-day rate of death or MI (15% versus 3.6%; \( P < 0.0001 \)), or death, MI, or recurrent angina with ECG changes (22.3% versus 6%; \( P < 0.0001 \)).

**Clinical Outcomes**

Death, MI, and recurrent angina events are listed in Table 4. The 30-day composite end point of death or MI was significantly lower in the eptifibatide- and enoxaparin-treated group as compared with eptifibatide- and UFH-treated group (5% versus 9%; \( P = 0.031 \)) (Figure 2). The composite end point of death, MI, or recurrent angina with adjudicated 12-lead ECG changes tended to be lower in the enoxaparin group (9% versus 12.6%; \( P = 0.11 \)) (Figure 3). The composite end point of death, MI, or recurrent angina requiring urgent revascularization was similar in the two treatment groups (12.4% versus 12.6%; \( P = 0.93 \)).

**Discussion**

In this high-risk group of non–ST-segment elevation ACS patients receiving aspirin and the glycoprotein IIb/IIIa inhibitor eptifibatide, the addition of the LMWH enoxaparin as compared with UFH resulted in lower rates of major bleeding and recurrent ischemia during and immediately after treatment, and lower 30-day rates of the composite of death or MI.

**Figure 1.** Rate of ischemia detected by 7-lead, 3-channel continuous ECG monitoring through the initial 48 hours and subsequent 48 to 96 hours after randomization.

**Figure 2.** Kaplan-Meier curves for prespecified secondary outcome of death or nonfatal myocardial (re)infarction during the first 30 days after randomization.

<table>
<thead>
<tr>
<th>Event</th>
<th>Eptifibatide and Enoxaparin (n=380)</th>
<th>Eptifibatide and UFH (n=366)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or (re)MI</td>
<td>19 (5.0)</td>
<td>33 (9.0)</td>
<td>0.031</td>
</tr>
<tr>
<td>MI peri-revascularization</td>
<td>2 (0.5)</td>
<td>7 (1.9)</td>
<td>0.10</td>
</tr>
<tr>
<td>Death, (re)MI, or RA with ECG changes</td>
<td>34 (9.0)</td>
<td>46 (12.6)</td>
<td>0.11</td>
</tr>
<tr>
<td>Death, (re)MI, or RA requiring urgent revascularization</td>
<td>53 (14.0)</td>
<td>59 (16.1)</td>
<td>0.41</td>
</tr>
<tr>
<td>Death</td>
<td>9 (2.4)</td>
<td>15 (4.1)</td>
<td>0.18</td>
</tr>
<tr>
<td>(Re)MI</td>
<td>15 (4.0)</td>
<td>21 (5.8)</td>
<td>0.25</td>
</tr>
<tr>
<td>RA with ECG changes</td>
<td>7 (1.8)</td>
<td>15 (4.1)</td>
<td>0.069</td>
</tr>
<tr>
<td>RA requiring urgent revascularization</td>
<td>28 (7.4)</td>
<td>20 (5.5)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Data are shown as n (%). RA denotes recurrent angina.
This is the largest randomized trial of combination glycoprotein IIb/IIIa inhibitor and LMWH therapy as part of initial medical management in a high-risk non–ST-elevation population to date and demonstrates that this combination is superior, not only as it relates to safety, but also in reducing objective ECG and clinical measures of ischemia. Previous studies demonstrating the value of IIb/IIIa inhibition have utilized UFH as the main antithrombotic therapy. The Antithrombotic Combination Using Tirofiban and Enoxaparin (ACUTE) II study, was a double-blind, randomized comparison of enoxaparin versus UFH in 525 patients with non–ST-segment ACS who were receiving aspirin and tirofiban. It demonstrated a similar safety profile (major hemorrhage 0.3% versus 1.0%) and 30-day rates of death (2.5% versus 6.0%) and nonfatal myocardial (re)infarction (3.2% versus 7.4%).

Figure 3. Kaplan-Meier curves for prespecified secondary outcome of death, nonfatal myocardial (re)infarction, or recurrent angina with ECG changes during the first 30 days after randomization.

Although our study was not powered to definitively address clinical outcomes, the lower rate of death or MI trend toward a lower incidence of death, MI, or recurrent angina with 12-lead ECG changes is consistent with the blinded continuous ECG monitoring findings in this and previous studies. In addition to being an important predictor of outcome, continuous ST-segment monitoring has identified superior antithromplatelet/thrombotic therapies in the management of non–ST-elevation ACS. Furthermore, the recurrence of ischemic events ("rebound") after UFH withdrawal portends a worse prognosis. Because combination aspirin, eptifibatide, and enoxaparin therapy resulted in significantly lower rates of recurrent ischemia (during initial management and after treatment withdrawal), it is not surprising that the incidence of manifest myocardial necrosis and death was also reduced.

Study Limitations

Our study was open label; however, the continuous ECG monitoring results were blinded, and all bleeding and clinical end points were adjudicated independently. The sample size was modest for evaluation of clinical outcomes, but the results are consistent with all previous comparisons of enoxaparin and UFH in the spectrum of ACS syndromes. Optimal management of high-risk non–ST-elevation ACS patients includes an early invasive strategy and the duration of combination therapy (48 hours) was shorter than the time to angiography (100 hours) and subsequent revascularization. Thus, the minority of patients in INTERACT received uninterrupted randomized treatment until the time of coronary angiography or revascularization. Therefore, the results of the Aggrastat to Zocor (A-to-Z) and Superior Yield of the New strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa inhibitors (SYNERGY) trials will better define the efficacy and safety of combination therapy in non–ST-elevation ACS patients managed with an early invasive approach.

In addition to aspirin, all patients in Fast Revascularization during InStability in Coronary artery disease (FRISC) II received LMWH therapy for 48 hours, and all patients in Treat angina with Aggrastat and determine Costs of Therapy with Invasive or Conservative Strategies (TACTICS) received UFH and glycoprotein IIb/IIIa inhibition.
before angiography; thus, even an invasive strategy requires initial medical management with potent antiplatelet/thrombolytic therapy. The role of clopidogrel has also been clearly established in non–ST-elevation ACS patients since our study was designed; hence, only 15% of patients received this therapy simultaneously. Although the benefit of initial treat-
ment with epftibatide and enoxaparin could presumably still be realized as part of a treatment strategy that included clopidogrel and an early invasive approach, the risk-benefit ratio of this approach remains unknown and warrants further study.

Conclusions
When aspirin and epftibatide are used in high-risk non–ST-
segment elevation ACS patients, enoxaparin improves out-
comes (determined on the basis of better safety and efficacy) compared with currently recommended UFH therapy and provides a useful novel alternative therapeutic strategy.

Appendix
The following persons participated in the INTERACT trial.

Steering Committee
Shaun Goodman (Principal Investigator), David Fitchett, Paul Arm-
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Data and Safety Monitoring Committee Co-Chairs
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sion; Royal Inland Hospital, Kamloops, British Columbia: Russell Reid, Lauren Kembel; Calgary Regional Health Authority, Calgary, Alberta: Peter Giannoccoro, Peggy Beresford; The Scarborough Hospital–Grace Division, Scarborough, Ontario: John Charles, Mary Bevins, Darlene Hutton; Vancouver Hospital & Health Science Center, Vancouver, British Columbia: John Jue, Denise Delane, Cheryl Davies, Heather Abbey, L. Tarry; Dr Georges-L Dumont Regional Hospital, Moncton, New Brunswick: Michel D’Astous, Marie-Claude Theriault; Misericordia Community Hospital & Health Center, Edmonton, Alberta: Paul V. Greenwood, Anne Prosser; Atlantic Health Sciences Corporation–Saint John Regional Hospital, Saint John, New Brunswick: James Ducharme, Kim Matheson.

Acknowledgments
This research was sponsored by the Canadian Heart Research Centre, Key Pharmaceuticals, Division of Schering Canada Inc, and Millen-
nium Pharmaceuticals Inc. Enoxaparin was provided by Aventis

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Circulation. published online January 13, 2003;
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

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