Safety and Efficacy of Enoxaparin vs Unfractionated Heparin in Patients With Non–ST-Segment Elevation Acute Coronary Syndromes Who Receive Tirofiban and Aspirin: A Randomized Controlled Trial

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IN RECENT YEARS, SEVERAL CLASSES of antiplatelet and antithrombotic agents have been shown to be safe and effective therapies for patients with non–ST-segment elevation acute coronary syndromes (ACS).1 Guidelines from the American College of Cardiology, American Heart Association, and European Society of Cardiology recommend early use of small-molecule platelet glycoprotein IIb/IIIa inhibitors with unfractionated heparin independently have shown superior efficacy over unfractionated heparin alone in patients with non–ST-elevation acute coronary syndromes (ACS). It is not clear if combining enoxaparin with glycoprotein IIb/IIIa inhibitors is as safe or as effective as the current standard combination of unfractionated heparin with glycoprotein IIb/IIIa inhibitors.

Objective To assess efficacy and safety of the combination of enoxaparin and tirofiban compared with unfractionated heparin and tirofiban in patients with non–ST-elevation ACS.

Design, Setting, and Participants A prospective, international, open-label, randomized, noninferiority trial of 1 mg/kg of enoxaparin every 12 hours (n=2026) compared with weight-adjusted intravenous unfractionated heparin (n=1961) in patients with non–ST-elevation ACS receiving tirofiban and aspirin. Phase A of the A to Z trial was conducted between December 1999 and May 2002.

Main Outcome Measures Death, recurrent myocardial infarction, or refractory ischemia at 7 days in the intent-to-treat population with boundaries set for superiority and noninferiority. Safety based on measures of bleeding using the Thrombolysis in Myocardial Infarction (TIMI) classification system.

Results A total of 169 (8.4%) of 2018 patients randomized to enoxaparin experienced death, myocardial infarction, or refractory ischemia at 7 days compared with 184 (9.4%) of 1952 patients randomized to unfractionated heparin (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.71-1.08). This met the prespecified criterion for noninferiority. All components of the composite primary and secondary end points favored enoxaparin except death, which occurred in only 1% of patients (23 for enoxaparin and 17 for unfractionated heparin). Rates for any TIMI grade bleeding were low (3.0% for enoxaparin and 2.2% for unfractionated heparin; P=.13). Using a worst-case approach that combined 2 independent bleeding evaluations, use of enoxaparin was associated with 1 additional TIMI major bleeding episode for each 200 patients treated.

Conclusions In patients receiving tirofiban and aspirin, enoxaparin is a suitable alternative to unfractionated heparin for treatment of non–ST-elevation ACS. The 12% relative and 1% absolute reductions in the primary end point in favor of enoxaparin met criterion for noninferiority and are consistent with prior trials performed without the use of glycoprotein IIb/IIIa inhibitors.

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These guidelines also support using low-molecular-weight heparins (LMWHs) in place of unfractionated heparin for patients with non–ST-segment elevation ACS as long as immediate coronary artery bypass graft surgery is not expected. Two large trials have shown the superiority of the LMWH enoxaparin over unfractionated heparin in patients with non–ST-segment elevation ACS. The major disadvantage of LMWH has been an increased rate of minor, but not major, bleeding. It is not clear if combining enoxaparin with glycoprotein IIb/IIIa inhibitors is as safe or effective as combining unfractionated heparin with glycoprotein IIb/IIIa inhibitors.

Therefore, we performed phase A of the A to Z trial to assess the efficacy and safety of enoxaparin with the glycoprotein IIb/IIIa inhibitor tirofiban compared with using unfractionated heparin with tirofiban in patients with ACS.

METHODS

The design of the A to Z trial has been described in detail in a previous publication. Briefly, the primary objective of phase A was to assess the safety and efficacy of enoxaparin compared with unfractionated heparin in patients with non–ST-segment elevation ACS who were receiving concomitant therapy with tirofiban and aspirin. Concurrently, phase A was to provide a cohort of optimally treated patients without non–ST-segment elevation ACS for enrollment into phase Z of the study to evaluate the efficacy and tolerability of early aggressive treatment with simvastatin compared with an accepted care regimen.

Patients

After local institutional review board approval of the protocol and written informed consent from patients, individuals with non–ST-segment elevation ACS who presented within 24 hours after onset of ischemic symptoms at rest were eligible for enrollment, provided the symptoms lasted at least 10 minutes and were associated with 0.5-mm ST-segment depression or higher, transient ST elevation of 1 mm or higher, or elevated cardiac markers (troponin or creatine kinase myocardial band at or above the upper limit of normal or, if a specific cardiac marker was not available, total creatine kinase twice the upper limit of normal). The exclusion criteria were nonischemic pain, shock, medical conditions precluding use of study drugs, ongoing use of lipid-lowering therapy, and poor trial candidacy. Key laboratory exclusions included total cholesterol of higher than 250 mg/dL (>6.48 mmol/L) and serum creatinine of higher than 2 mg/dL (>176.8 mmol/L).

Design

Phase A of the A to Z trial was an open-label, randomized, active study comparing enoxaparin with unfractionated heparin in patients receiving tirofiban and aspirin. Randomization was blinded through use of a simple, site-based allocation scheme that used sealed envelopes that corresponded to each patient number allocated to the site. The envelopes contained treatment assignments generated using a simple randomization procedure without blocking.

Open-label therapy consisted of enoxaparin (1 mg/kg every 12 hours) or weight-adjusted unfractionated heparin. The suggested unfractionated heparin dosage was based on previous guidelines from the American College of Cardiology and the American Heart Association (patients weighing ≥70 kg: 4000-U intravenous bolus, followed by 900-U infusion per hour; patients weighing <70 kg, 60-U/kg [maximum 4000 U] bolus followed by 12-U/kg infusion per hour). Unfractionated heparin was titrated to achieve an activated partial thromboplastin time of 50 to 70 seconds using an algorithm provided to the investigators.

All patients were required to receive tirofiban and aspirin. The dosing regimen for tirofiban in the A to Z trial was a hybrid between the previously proven ACS and percutaneous coronary intervention dosing regimens: a bolus of 10 mg/kg over 3 minutes, followed by a maintenance infusion of 0.1 mg/kg per minute for a suggested minimum of 48 hours (or a minimum of 12 hours after intervention) and a maximum of 120 hours. Initial dosages of aspirin were 150 to 325 mg/d, followed by a daily dose of 75 to 325 mg/d throughout treatment.

The overall management strategy of early invasive (intent to pursue catheterization within 108 hours) compared with early conservative (initial medical management without planned catheterization) was at the discretion of local investigators. Investigators were to designate their strategy at enrollment. Tirofiban could be discontinued 12 hours after percutaneous coronary intervention. Patients randomized to enoxaparin were permitted to be switched to unfractionated heparin for invasive procedures.

Follow-up for end points was at 30 days for all patients and consisted of a visit for patients randomized into phase Z or telephone contact for those who were ineligible or declined to participate in phase Z.

End Points

The primary end point was a composite of all-cause death, new myocardial infarction (MI; an increase in a cardiac marker to >2 times the upper limit of normal or an increase of >50% in a marker associated with symptoms of ischemia), or refractory ischemia within 7 days of tirofiban initiation. Refractory ischemia required recurrent symptoms and electrocardiographic changes or elevation in cardiac markers. All-cause death, MI, refractory ischemia, urgent coronary revascularization, and documented multiple clinical myocardial ischemic events were evaluated at 7 days individually and as a composite. Multiple clinical myocardial ischemic events were defined as chest pain requiring a change in therapy but not meeting criteria for refractory ischemia. Tertiary end points were evalu-
Safety

Bleeding events were collected from enrollment until 24 hours after completion of the tirofiban infusion. First, an investigator assessment was collected on the case report form; additionally, an independent, retrospective, blinded, central assessment of bleeding was performed, capturing hemoglobin values at baseline and day 1, the nadir value, and values before and after any cardiac catheterization or percutaneous coronary intervention. Second, units of packed red blood cells transfused were also captured. Patient data were censored for bleeding and transfusion on the day of coronary artery bypass graft surgery if performed. Bleeding events identified by either the investigator assessment or the central assessment were combined using a worst-case approach in the final bleeding report. Bleeding events were categorized by the change in hemoglobin using the Thrombolysis in Myocardial Infarction (TIMI) criteria. Major bleeding required a decrease in hemoglobin of more than 5 mg/dL or intracranial or pericardial bleeding. Minor bleeding consisted of a decrease in hemoglobin between more than 3 mg/dL and 5 mg/dL with a documented site or hematoma, hematochezia, or hemateme sia. Each unit of transfusion was counted as equivalent to 1 mg/dL of a hemoglobin drop. An independent data and safety monitoring committee oversaw safety. Two interim analyses were performed; neither met the Lan-DeMets implementation of the O'Brien-Fleming stopping boundaries.

Statistical Design and Analysis

Phase A was designed as a noninferiority study. Primary statistical analysis was performed by the Duke Clinical Research Institute with confirmation by the sponsor (Merck). To estimate the power and noninferiority margin at the time of study inception, data from the most pertinent related study (Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms [PRISM-PLUS]) was used. A 12.9% event rate was projected in the group receiving unfractionated heparin and tirofiban. A 10% treatment effect of enoxaparin was assumed based on prior studies comparing enoxaparin with unfractionated heparin. An original proposed sample size of 5200 patients provided 89% power to meet the noninferiority boundary, specified as follows: enoxaparin was to be considered noninferior to unfractionated heparin if the upper 1-sided 95% confidence boundary (CI) for the enoxaparin effect relative to unfractionated heparin was less than 1.14. The origin of the margin is from PRISM-PLUS, in which the odds ratio (OR) for death, MI, or refractory ischemia was 0.66 for the combination of tirofiban and unfractionated heparin compared with unfractionated heparin alone. Taking the inverse of the upper bound of the 95% CI yielded the noninferiority margin of 1.14. Similar power calculations for the study with a sample size of 4000 patients yielded a probability of 81% for obtaining an upper 95% confidence bound of less than 1.14.

The primary analysis was a time-to-event analysis performed on the intent-to-treat population that consisted of all randomized patients. Six of the 3987 randomized patients had no data due to lost records at 2 sites (4 patients at one site and 2 patients at another site). Two additional populations were prespecified to support or refute a finding of noninferiority: the population receiving treatment (n = 3719; patients received tirofiban and at least 1 dose of randomized treatment within 12 hours of enrollment); and patients who were conservatively managed (n = 1506; patients not undergoing coronary angiography or percutaneous coronary intervention within 108 hours of randomization). Internal consistency for these additional populations was defined by the point estimate of efficacy rather than the upper bound of the 95% CIs because the specifications reduced their sample sizes. Analyses were based on Cox proportional hazards models. Covariates included treat-
ENOXAPARIN VS UNFRACTIONATED HEPARIN

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Enoxaparin (n = 2026)</th>
<th>Unfractionated Heparin (n = 1961)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (25th-75th percentiles), y</td>
<td>61 (52-69)</td>
<td>61 (53-69)</td>
<td>.59</td>
</tr>
<tr>
<td>Men, No./total (%)</td>
<td>1445/2026 (71.4)</td>
<td>1391/1955 (71.2)</td>
<td>.89</td>
</tr>
<tr>
<td>Race, No./total (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1733/2025 (85.6)</td>
<td>1665/1955 (85.2)</td>
<td>.53</td>
</tr>
<tr>
<td>Black</td>
<td>65/2026 (3.2)</td>
<td>64/1955 (3.3)</td>
<td>.89*</td>
</tr>
<tr>
<td>Asian</td>
<td>85/2025 (4.2)</td>
<td>86/1954 (4.4)</td>
<td>.74†</td>
</tr>
<tr>
<td>Prior cardiovascular history, No./total (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina (past 6 weeks)</td>
<td>1176/2022 (58.2)</td>
<td>1080/1955 (55.2)</td>
<td>.06</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>360/2022 (17.8)</td>
<td>357/1955 (18.3)</td>
<td>.71</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>185/2022 (9.1)</td>
<td>191/1954 (9.8)</td>
<td>.50</td>
</tr>
<tr>
<td>Coronary artery bypass graft surgery</td>
<td>95/2026 (4.7)</td>
<td>105/1961 (5.4)</td>
<td>.34</td>
</tr>
<tr>
<td>Percutaneous intervention</td>
<td>86/2026 (4.2)</td>
<td>87/1961 (4.4)</td>
<td>.77</td>
</tr>
<tr>
<td>Stent</td>
<td>51/2026 (2.5)</td>
<td>43/1961 (2.2)</td>
<td>.50</td>
</tr>
<tr>
<td>Risk factors, No./total (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>131/2022 (6.5)</td>
<td>125/1955 (6.9)</td>
<td>.59</td>
</tr>
<tr>
<td>Diabetes</td>
<td>395/2022 (19.5)</td>
<td>356/1954 (18.2)</td>
<td>.29</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1012/2022 (50.0)</td>
<td>1022/1955 (52.3)</td>
<td>.16</td>
</tr>
<tr>
<td>Current smoking</td>
<td>728/2021 (36.0)</td>
<td>789/1952 (39.4)</td>
<td>.03</td>
</tr>
<tr>
<td>Congestive heart failure (&lt;6 weeks)</td>
<td>136/2022 (6.7)</td>
<td>114/1955 (5.8)</td>
<td>.24</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>221/2021 (10.9)</td>
<td>218/1954 (11.2)</td>
<td>.82</td>
</tr>
<tr>
<td>Prior medications, No./total (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>497/2022 (24.6)</td>
<td>498/1954 (25.5)</td>
<td>.51</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>1010/2021 (50.0)</td>
<td>1001/1954 (51.2)</td>
<td>.43</td>
</tr>
<tr>
<td>Nitrates</td>
<td>1381/2022 (68.3)</td>
<td>1321/1955 (67.6)</td>
<td>.62</td>
</tr>
<tr>
<td>Diuretics</td>
<td>313/2021 (15.5)</td>
<td>309/1954 (15.8)</td>
<td>.84</td>
</tr>
<tr>
<td>Long-term aspirin</td>
<td>825/1909 (40.9)</td>
<td>800/1953 (41.0)</td>
<td>.95</td>
</tr>
<tr>
<td>Unfractionated heparin before randomization</td>
<td>755/2023 (37.3)</td>
<td>753/1955 (38.5)</td>
<td>.44</td>
</tr>
<tr>
<td>LMWH before randomization</td>
<td>693/2023 (34.3)</td>
<td>688/1955 (34.2)</td>
<td>.95</td>
</tr>
<tr>
<td>Neither unfractionated nor LMWH</td>
<td>630/2023 (31.1)</td>
<td>591/1955 (30.2)</td>
<td>.53</td>
</tr>
<tr>
<td>Qualifying event, No./total (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigator-determined myocardial infarction</td>
<td>1504/2020 (74.5)</td>
<td>1423/1955 (72.8)</td>
<td>.23</td>
</tr>
<tr>
<td>Elevated cardiac marker</td>
<td>1479/1842 (80.3)</td>
<td>1405/1764 (79.7)</td>
<td>.63</td>
</tr>
<tr>
<td>ST change &gt;1 mm</td>
<td>1409/2003 (70.3)</td>
<td>1393/1937 (71.9)</td>
<td>.28</td>
</tr>
</tbody>
</table>

Abbreviation: LMWH, low-molecular-weight heparin. *Comparison for blacks vs whites. †Comparison for Asians vs whites.

Table 2. Hospital Course

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Enoxaparin (n = 2026)</th>
<th>Unfractionated Heparin (n = 1961)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study drug administration, median (25th-75th percentiles), h</td>
<td>49.1 (12-96)</td>
<td>48.2 (36.3-70.8)</td>
</tr>
<tr>
<td>Investigator-declared invasive intent, No./total (%)</td>
<td>1115/2021 (55.2)</td>
<td>1083/1955 (55.4)</td>
</tr>
<tr>
<td>Catheterization or PCI, No./total (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 48 h</td>
<td>861/2026 (42.5)</td>
<td>858/1961 (43.8)</td>
</tr>
<tr>
<td>Within 108 h</td>
<td>1208/2026 (59.6)</td>
<td>1202/1961 (61.3)</td>
</tr>
<tr>
<td>Discharge medications, No./total (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>871/2020 (43.1)</td>
<td>862/1954 (44.1)</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>48/2020 (2.4)</td>
<td>76/1954 (3.9)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>1714/2020 (84.9)</td>
<td>1635/1954 (83.7)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>1642/1909 (81.3)</td>
<td>1642/1954 (84.0)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>435/2019 (21.5)</td>
<td>448/1954 (22.9)</td>
</tr>
<tr>
<td>Potassium-sparing diuretic</td>
<td>76/1909 (3.8)</td>
<td>72/1952 (3.7)</td>
</tr>
<tr>
<td>Other diuretics</td>
<td>368/1909 (18.2)</td>
<td>388/1952 (19.9)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1997/2020 (98.9)</td>
<td>1923/1954 (98.4)</td>
</tr>
</tbody>
</table>

Abbreviation: PCI, percutaneous coronary intervention.

RESULTS

There were 3987 patients enrolled into phase A from 340 sites in 41 countries between December 1999 and May 2002. Enrollment was halted short of its original enrollment goal of 5200 patients in May 2002 because enrollment into phase Z of the trial was nearing completion. Most patients were recruited from Europe and the United States. Approximately two thirds (2583/3987) of those enrolled continued in phase Z. The remainder completed the study after telephone follow-up at 30 days. Follow-up for the primary 7-day end point was complete for more than 99.5% of patients (FIGURE 1).

Baseline characteristics were well balanced between the treatment groups (TABLE 1). Investigators classified more than 2927 patients (74%) as having non-ST-segment elevation MI at presentation. Elevations in troponin or creatine kinase myocardial bands were found in 3190 (80%) of those enrolled. Only 1221 patients (30.7%) enrolled received neither unfractionated heparin nor LMWH before enrollment.

Key characteristics of the hospital course are shown in TABLE 2. An early invasive treatment strategy was declared for 1115 (55.2%) of 2021 patients randomized to enoxaparin and for 1083 (55.4%) of 1955 patients randomized to unfractionated heparin. By 48 hours, 861 (42.5%) of 2026 patients in the as-treated population (n=3906), in which patients were assigned to the enoxaparin group (n=1941) or the unfractionated heparin group (n=1965) based on actual treatment received. Those who received both treatments were analyzed in their original group at randomization. The Fisher exact test was used to compare differences in TIMI bleeding categories and other adverse events, including use of transfusions and incidence of thrombocytopenia. Statistical analyses were performed using SAS software (version 8, SAS Institute Inc, Cary, NC).
the enoxaparin group and 858 (43.8%) of 1961 patients in the unfractionated heparin group had undergone catheterization. Median duration of drug use was 49.1 hours for enoxaparin and 48.2 hours for unfractionated heparin.

**Efficacy**

A total of 3970 patients had complete data or an end point through 7 days (Figure 2). Crude event rates were 8.4% (169/1982) for enoxaparin and 9.4% (184/1992) for unfractionated heparin (hazard ratio [HR], 0.88; 95% CI, 0.71-1.08). This 1% absolute and 12% relative benefit favoring enoxaparin met the prespecified noninferiority margin. The primary combined end point analysis for the supportive populations revealed consistent results with HRs favoring enoxaparin. In the population receiving treatment, the crude event rates were 8.6% (157/1836) for enoxaparin and 9.5% (178/1875) for unfractionated heparin (HR, 0.89; 95% CI, 0.72-1.11). For the conservatively managed population receiving treatment, the crude event rates were 6.7% (52/773) for enoxaparin and 8.0% (58/728) for unfractionated heparin (HR, 0.85; 95% CI, 0.58-1.23). Similarly, the composite secondary end point at 7 days (which added urgent revascularization and clinical ischemia) showed a trend in favor of enoxaparin (HR, 0.89; 95% CI, 0.75-1.05). All components of this composite numerically favored enoxaparin except death, which occurred in only 1.1% of patients (n = 23) receiving enoxaparin and 0.9% of patients receiving unfractionated heparin (n = 17; Table 3).

Figure 3 shows the HRs for various subgroups of the intent-to-treat population. The point estimate for enoxaparin was favorable in nearly all of the higher risk subgroups with no significant interactions observed. Analyses accounting for prerandomization antiplatelet use are shown in Figure 4. There was a tendency whereby enoxaparin was associated with a lower risk of the primary end point when no prior antiplatelet had been administered (HR, 0.77; 95% CI, 0.53-1.11; P = .38 for interaction).

**Safety**

Transfusion rates in the trial were 0.9% overall with no difference between randomized treatment groups. For the as treated population, 19 (1.0%) of 1941 patients in the enoxaparin group and 16 (0.8%) of 1965 patients in the unfractionated heparin group received packed red blood cell transfusions. The incidence of in-hospital platelet counts of less than 100 × 10^9/L were 1.2% (23/1936) with enoxaparin and 1.5% (30/1961) with unfractionated heparin. One patient in the enoxaparin group and 6 patients in the unfractionated heparin group had platelet counts of less than 20 × 10^9/L.

Combined rates of clinically significant bleeding (TIMI major or minor bleeding) in the as-treated population were 3.0% (59/1940) in the enoxaparin group vs 2.2% (44/1965) in the unfractionated heparin group (P = .13). A worst-case analysis for TIMI major bleeding revealed an increased frequency of approximately 1 in 200 associated with use of enoxaparin (0.9% [n = 18] vs 0.4% with unfractionated heparin [n = 8]; P = .05). Further breakdown of major bleeding in the as treated population revealed no difference in investigator-reported rates of major bleeding (0.4% [n = 8] for enoxaparin vs 0.3% [n = 5] for unfractionated heparin; P = .42) whereas there was a significant difference in major bleeding identified by the independent assessment (0.8% [n = 15] vs 0.2% [n = 4], respectively; P = .01). There were no differences in major bleeding rates between enoxaparin and unfractionated heparin for individuals who underwent early intervention. However, there was a significant increase in reports of “any bleed” driven primarily by investigator-generated reports.

**Table 3. Secondary End Points**

<table>
<thead>
<tr>
<th>End Point</th>
<th>No./Total (% of Patients With End Point</th>
<th>Enoxaparin (n = 2026)</th>
<th>Unfractionated Heparin (n = 1961)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>23/2024 (1.1)</td>
<td>17/1957 (0.9)</td>
<td>1.26 (0.67-2.38)</td>
<td>.47</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>73/1998 (3.6)</td>
<td>86/1938 (4.4)</td>
<td>0.82 (0.60-1.13)</td>
<td>.23</td>
<td></td>
</tr>
<tr>
<td>Refractory ischemia</td>
<td>81/1997 (4.1)</td>
<td>95/1937 (4.9)</td>
<td>0.82 (0.61-1.10)</td>
<td>.19</td>
<td></td>
</tr>
<tr>
<td>Urgent revascularization</td>
<td>103/1992 (5.1)</td>
<td>101/1926 (5.2)</td>
<td>0.98 (0.74-1.29)</td>
<td>.89</td>
<td></td>
</tr>
<tr>
<td>Documented multiple clinical myocardial ischemic events*</td>
<td>22/1985 (1.1)</td>
<td>37/1927 (1.9)</td>
<td>0.58 (0.34-0.98)</td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>Composite</td>
<td>255/2006 (12.7)</td>
<td>275/1937 (14.2)</td>
<td>0.89 (0.75-1.05)</td>
<td>.16</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

*Indicates chest pain requiring change in therapy but not meeting criteria for refractory ischemia.

*TABLE 4. A worst-case analysis for TIMI major bleeding revealed an increased frequency of approximately 1 in 200 associated with use of enoxaparin (0.9% [n = 18] vs 0.4% with unfractionated heparin [n = 8]; P = .05). Further breakdown of major bleeding in the as treated population revealed no difference in investigator-reported rates of major bleeding (0.4% [n = 8] for enoxaparin vs 0.3% [n = 5] for unfractionated heparin; P = .42) whereas there was a significant difference in major bleeding identified by the independent assessment (0.8% [n = 15] vs 0.2% [n = 4], respectively; P = .01). There were no differences in major bleeding rates between enoxaparin and unfractionated heparin for individuals who underwent early intervention. However, there was a significant increase in reports of “any bleed” driven primarily by investigator-generated reports.*

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identified minor bleeding episodes. Exposure from one form of pretreatment heparin to another at randomization was not associated with increased risk of bleeding. Exposure to a different form of heparin after randomization was more common for patients receiving enoxaparin (275/1940) than those receiving unfractionated heparin (62/1965). Among the patients initially receiving enoxaparin, overall major or minor bleeding occurred in 3.0% (50/1665) of patients who received enoxaparin alone compared with 3.3% (9/275) for those who were crossed over to unfractionated heparin after primary treatment with enoxparin. Bleeding rates in the intent-to-treat population were similar to those in the as treated population.

**COMMENT**

Analysis of the 3987 patients randomized into phase A of the A to Z trial revealed a 1% absolute and 12% relative difference in favor of enoxaparin compared with unfractionated heparin for the prevention of the composite end point of death, MI, or refractory ischemia. This benefit did not meet criteria to declare superiority but fell well within specified bounds for noninferiority. We found a consistent but non-significant risk reduction of 10% to 15% with enoxaparin across various subpopulations and most subgroups. These risk reductions were of a larger magnitude for patients at higher risk, those who were being managed conservatively, and those who received no antithrombotic agent within 24 hours before randomization. These trends should be interpreted with caution in the absence of a finding of superiority; however, they are consistent with prior studies of glycoprotein IIb/IIIa inhibition with tirofiban and studies comparing enoxaparin with unfractionated heparin, which found greater relative efficacy among higher risk patients.16-19

As the options for antiplatelet and antithrombotic treatment evolve, it is important to understand how best to integrate these treatments into the care of patients with non–ST-segment el-

**Figure 3. Effects of Enoxaparin Compared With Unfractionated Heparin Among Subgroups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No./Total No. (%)</th>
<th>Favors Enoxaparin</th>
<th>Favors Unfractionated Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (&lt;65 vs ≥65)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>78/1213 (6.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfractionated Heparin</td>
<td>85/1155 (7.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y (&lt;65 vs ≥65)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>119/1438 (8.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>50/580 (8.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33/396 (8.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>139/1620 (8.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>28/420 (6.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-United States</td>
<td>141/1588 (8.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early Invasive</td>
<td>96/1111 (8.8)</td>
<td></td>
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</tr>
<tr>
<td>Early Conservative</td>
<td>70/904 (7.7)</td>
<td></td>
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</tr>
<tr>
<td>ST Change ≥1 mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>125/1403 (9.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST Change ≥1 mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>42/593 (7.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troponin Level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>27/334 (8.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>89/1072 (8.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI Risk Score</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0-2</td>
<td>54/846 (6.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td>72/888 (8.1)</td>
<td></td>
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</tr>
<tr>
<td>5-7</td>
<td>43/284 (15.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>169/2018 (8.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4. Prerandomization Treatment With Unfractionated Heparin, Low-Molecular-Weight Heparin, or No Antithrombin**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No./Total No. (%)</th>
<th>Favors Enoxaparin</th>
<th>Favors Unfractionated Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Unfractionated Heparin Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (Only Unfractionated Heparin)</td>
<td>62/750 (8.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (LMWH or No Antithrombin)</td>
<td>107/1268 (8.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior LMWH Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (Only LMWH)</td>
<td>59/691 (8.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (Unfractionated Heparin or LMWH)</td>
<td>110/1235 (8.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Unfractionated Heparin or LMWH Use</td>
<td>118/1386 (8.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (No Prior Antithrombin)</td>
<td>51/630 (8.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LMWH indicates low-molecular-weight heparin.
evolution ACS. Previous trials comparing unfractionated heparin and enoxaparin as adjunctive therapy to tirofiban in patients with non–ST-segment elevation ACS were designed to examine safety and were not adequately powered for clinical outcomes. In the second Antithrombotic Combination Using Tirofiban and Enoxaparin (ACUTE II) trial, enoxaparin was associated with significantly reduced rates of refractory ischemia requiring urgent revascularization and rehospitalization for unstable angina. This latter end point did not require objective evidence of ischemia and may correlate with the strong trend toward reduced recurrent clinical ischemia seen with enoxaparin in the present trial. The Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment (INTERACT) trial compared enoxaparin with unfractionated heparin in combination with epifibatide and aspirin in 746 patients. Approximately the first third of the patients enrolled in INTERACT were prohibited from receiving prior antithrombotic therapy, and, for the trial, the average duration of prior antithrombotic use was only 4 hours. At 7 days in INTERACT, enoxaparin showed a benefit of 38% for the composite end point of death or MI and 19% for the composite end point of death, MI, or electrocardiographic changes (Shaun Goodman, written communication, March 2003). In phase A of the A to Z trial, patients randomized to receive enoxaparin who had not received prior antithrombin treatment had a 23% lower rate of the composite triple end point at 7 days than did similar patients randomized to receive unfractionated heparin.

The 9.4% composite event rate in the unfractionated heparin group of the current study was lower than the anticipated rate derived from the Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-Wave MI (ESSENCE) trial (23.3%) and TIMI 11B (14.5%), and similar to that seen in INTERACT (9.8%). This may reflect differences in both patient characteristics and adherence to guideline-based therapies, which was high in the present study. The use of glycoprotein IIb/IIIa inhibitors in all patients enrolled in phase A of the A to Z trial and in the INTERACT trial may also have contributed to the lower event rates in the unfractionated heparin groups in both of these trials. Additionally, the phase A population was approximately 3 years younger and comprised fewer patients with prior MI than previous cohorts. The exclusion of patients with prior use of statin agents (to permit enrollment into phase Z) likely contributed to enrollment of patients with lower risk characteristics.

**Safety**

Despite high rates of invasive therapy and the use of potent antiplatelet and antithrombotic therapies, the overall rates of bleeding, transfusion, and thrombocytopenia were low in both heparin groups. Major bleeding in this trial was somewhat higher than in 2 previous trials (ACUTE II and INTERACT) designed to assess the safety of the combination of a glycoprotein IIb/IIIa inhibitor and enoxaparin, but there were

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The A to Z trial compared with previ-
ous coronary artery bypass graft surgery found in phase A of the A to Z trial compared with previous trials is reassuring (Table 5).6.9.10 There were statistical trends for increased bleeding with use of enoxaparin in this trial, but the absolute increment in bleeding risk was low. For major bleeding, this risk was less than 1.6 in 1000 for physician-identified major bleeding and 6 in 1000 for 1 event of major bleeding as identified by a drop in hemoglobin of greater than 5 mg/dL. The discrepancy between the rates identified by 2 bleeding assessments highlights the importance of defining the methods for determining rates and the ambiguity associated with assigning clinical relevance to borderline statistical trends when event rates are low. In this trial, the low rate of transfusion combined with the lack of a corresponding difference in transfusion rates between the groups further diminishes the clinical relevance of the trends for increased bleeding with enoxaparin. This discordance in trends toward significance between bleeding and transfusion rates among the agents may be attributable to the method used to classify bleeding (hemoglobin change vs identification of a clinical event), or to the low dosage of unfractionated heparin (4000-U bolus and 900-U initial infusion maximum, recommended for use with tirofiban).

**Limitations**

The open-label design of this investigation is the most serious limitation. Knowledge of study drug might have affected numerous clinical decisions regarding early treatment, especially whether or not to pursue an invasive course. This could have induced selection bias with respect to determinations of both efficacy and safety despite the observed balance between rates and timing of catheterization and percutaneous coronary intervention between the 2 study groups. The study was not designed to definitively address the key issue of efficacy and safety of enoxaparin during early intervention because it allowed the use of unfractionated heparin at the time of catheterization in patients randomized to enoxaparin—a process commonly used in practice. This question is being addressed in the larger, more specifically designed Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial.20 Our study design allowed individuals who were treated within 24 hours of antithrombin to enter the trial, a feature that could have influenced the results.

The independent bleeding assessment collection was retrospective and was not part of the original protocol, but was an appropriate response to the low rate of investigator-reported bleeding seen during the monitoring phase of the trial. Finally, the trial did not systematically capture data regarding the use of clopidogrel, and thus cannot determine the incremental risks or benefits of using clopidogrel.

**Clinical Implications**

The present findings support the use of enoxaparin as an effective noninferior alternative to unfractionated heparin in patients with high-risk non–ST-segment elevation ACS eligible for treatment with a glycoprotein IIb/IIIa antagonist. These benefits have to be weighed against possible effects associated with the use of enoxaparin, given its longer half-life and limitations in patient subgroups, such as those with impaired renal function and those who may require full and rapid reversal of anticoagulation (ie, patients receiving coronary artery bypass graft surgery). We observed a 1 in 200 increased risk for major bleeding with enoxaparin. The clinical relevance of this finding is low and is further diminished by the absence of any associated increase in transfusion rates. Because it is easier to use and modestly reduces recurrent ischemic events without an increase in the need for blood products, enoxaparin compares favorably with unfractionated heparin in patients with non–ST-segment elevation ACS who are receiving tirofiban and aspirin.

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ENOXAPARIN VS UNFRACTIONATED HEPARIN

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individuals already infected with HIV should thus continue vigil- 
ant personal protection through safe-sex practices or clean 
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CORRECTIONS

Incorrect Dosages: In the Original Contribution entitled “Safety and Efficacy of 
Enoxaparin vs Unfractionated Heparin in Patients With Non–ST-Segment Eleva-
tion Acute Coronary Syndromes Who Receive Tirofiban and Aspirin: A Random-
ized Controlled Trial” published in the July 7, 2004, issue of JAMA (2004;292:55-64),
there were 2 incorrect dosages on page 56. At the bottom of column 2, the sen-
tence should read, “The dosing regimen for tirofiban in the A to Z trial was a hy-
brid between the previously proven ACS and percutaneous coronary intervention 
dosing regimens: a bolus of 10 µg/kg over 3 minutes, followed by a maintenance 
infusion of 0.1 µg/kg per minute for a suggested minimum of 48 hours (or a mini-
imum of 12 hours after intervention) and a maximum of 120 hours.9,13”

Funding Source Omitted: In the Original Contribution entitled “Association Be-
tween Youth-Focused Firearm Laws and Youth Suicides” published in the August 
4, 2004, issue of JAMA (2004;292:594-601), a funding source was omitted. In 
addition to the sources cited, the study also received support from the David and 
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