Low-Molecular-Weight Heparins in the Management of Acute Coronary Syndromes

Peter J. Zed, PharmD; James E. Tisdale, PharmD; Steven Borzak, MD

Acute coronary syndromes (unstable angina and non-Q-wave myocardial infarction) are caused by the rupture of an atherosclerotic plaque, platelet activation, and fibrin deposition resulting in thrombosis. Aspirin and unfractionated heparin have traditionally been the treatments of choice for patients with acute coronary syndromes. Low-molecular-weight heparins offer potential advantages over unfractionated heparin, having proven equally effective for the treatment and prevention of many thromboembolic processes. Recently, a number of randomized controlled trials have been conducted to evaluate the role of low-molecular-weight heparins in the management of patients with unstable angina or non–Q-wave myocardial infarction. The purpose of this article is to review and evaluate the available literature on the use of low-molecular-weight heparins in the management of acute coronary syndromes to establish their role in therapy.

Arch Intern Med. 1999;159:1849-1857

The initiating event of the acute coronary syndromes (unstable angina and non–Q-wave myocardial infarction) involves the rupture of an atherosclerotic plaque resulting in the platelet activation and fibrin deposition that leads to thrombosis. Evidence that both platelet activation and thrombin generation are involved in the thrombotic process provides a rationale for the use of both aspirin and unfractionated heparin (UFH) in the management of acute coronary syndromes. There has been much research and debate in the past decade on the value of these agents alone or in combination. Aspirin and UFH have become the standard practice for treatment of patients presenting with unstable angina or non–Q-wave myocardial infarction. Low-molecular-weight heparins (LMWHs) have recently been marketed in North America and offer potential advantages over UFH. The purpose of this article is to review and evaluate the available literature on the use of LMWHs in the management of acute coronary syndromes and to provide recommendations for their role in therapy.

UNFRACTIONATED HEPARIN

Unfractionated heparin is a heterogeneous polydispersed mixture of sulfated polysaccharides ranging in molecular weight from 5000 to 30 000 d (average molecular weight, 12 000-15 000 d). Its major anticoagulant effect is attributed to a unique pentasaccharide sequence with high affinity for antithrombin III (ATIII). Binding of heparin to ATIII produces a conformational change in this protein, accelerating the ability to inactivate the coagulation enzymes thrombin (factor IIa), factor Xa, and factor IXa. Of these 3 enzymes, thrombin is the most sensitive to inhibition by the heparin/ATIII complex. Unfractionated heparin accelerates the inactivation of thrombin by ATIII by acting as a template to which both the enzyme and the inhibitor bind to form a ternary complex. In contrast, the inactivation of factor Xa does not require a ternary complex and is achieved by binding directly to ATIII. The ability of UFH to
Inhibit thrombin is dependent on saccharide chain length and ultimately molecular weight. Thus, UFH molecules that contain fewer than 18 saccharide units are unable to bind thrombin and ATIII simultaneously and therefore are unable to accelerate the inactivation of thrombin. However, they do retain their ability to catalyze the inactivation of factor Xa.14-15

Unfractionated heparin is not absorbed following oral administration and therefore must be given by intravenous (IV) or subcutaneous (SC) injection. The efficacy and safety of UFH when administered by either continuous IV infusion or by the SC route are comparable provided that the doses are adequate.16 Following its injection and passage into the bloodstream, UFH binds to a number of plasma proteins including histidine-rich glycoprotein, platelet factor 4, vitronectin, fibronectin, and von Willebrand factor.9 The binding of UFH to these proteins results in reduced bioavailability, variable anticoagulant response, and the phenomenon known as heparin resistance.17 Unfractionated heparin also binds to macrophages and endothelial cells, another reason for its complicated pharmacokinetics. Unfractionated heparin is cleared through the combination of a rapid, concentration-dependent (saturable) mechanism and a much slower nonsaturable mechanism. The concentration-dependent mechanism results from UFH binding to macrophages and endothelial cells. Clearance through the much slower nonsaturable mechanism is partially through renal excretion. The apparent biological half-life of UFH is dose dependent, increasing from 30 minutes with an IV bolus of 25 U/kg, to 60 minutes with an IV bolus of 100 U/kg, to 150 minutes with an IV bolus of 400 U/kg.18,19

The anticoagulant effect of UFH is traditionally monitored by the activated partial thromboplastin time (aPTT), which is sensitive to the inhibitory effect of UFH on thrombin, factor Xa, and factor IXa. Therapeutic ranges are typically 1.5 to 2.5 times baseline aPTT.9 Alternatively, UFH treatment can be monitored by a chromatographic antifactor Xa heparin assay with a targeted range of 0.3 to 0.7 U/mL.9

Administration of UFH is associated with some disadvantages. The interpatient variability of anticoagulant response is thought to be due to the interindividual differences in concentrations of heparin-neutralizing plasma proteins, as well as variable elevations of factor VIII as part of the acute-phase reaction response to ischemia.9 Bleeding is the most common complication of UFH therapy; UFH has the potential to induce bleeding by inhibiting blood coagulation, impairing platelet function, and increasing capillary permeability.9 Heparin-induced thrombocytopenia occurs in approximately 3% to 4% of heparin-treated patients.20-22 It is an immunoglobulin-mediated adverse drug reaction associated with a high risk for thrombotic complications. The pathogenic antibody, usually IgG, recognizes a multimolecular complex of heparin and platelet factor 4 resulting in platelet activation.22-23 Finally, osteoporosis has been associated with high-dose, long-term UFH therapy.24-27

**LOW-MOLECULAR-WEIGHT HEPARINS**

Low-molecular-weight heparins are produced by enzymatic or chemical depolymerization of UFH to yield chains with molecular weights ranging from 4000 to 6500 daltons, with an average molecular weight of 5000 daltons (15 saccharide units).28-30 (Table 1). Owing to their small molecular size, LMWHs have a reduced ability to catalyze the inactivation of factor Xa. Thus, compared with UFH, which has an antifactor Xa–antifactor IIa ratio of 1:1, LMWHs have an antifactor Xa–antifactor IIa ratio of between 4:1 and 2:1 (Table 2). The relative importance of inhibition of factor Xa and thrombin in mediating the antithrombotic effect of UFH and LMWHs is unclear, but there is evidence that they are both necessary.11,12,32 In addition, the reduced protein binding of LMWHs improves their pharmacokinetic properties, and a minimal interaction with platelets could be responsible for the reduced microvascular bleeding and lower incidence of heparin-induced thrombocytopenia.28,29

<table>
<thead>
<tr>
<th>LMWH</th>
<th>Method of Preparation</th>
<th>Mean Molecular Weight, d</th>
<th>Anti-Xa/Anti-lla Ratio</th>
<th>Half-life, h*</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin (Lovenox)</td>
<td>Benzylation and alkaline depolymerization</td>
<td>4200</td>
<td>3.8:1</td>
<td>2.2-6.0</td>
<td>Canada/United States</td>
</tr>
<tr>
<td>Dalteparin (Fraxiparin)</td>
<td>Nitrous acid depolymerization</td>
<td>6000</td>
<td>2.7:1</td>
<td>2.0-5.0</td>
<td>Canada/United States</td>
</tr>
<tr>
<td>Tinzaparin (Innohep)</td>
<td>Heparinase digestion</td>
<td>4000</td>
<td>1.9:1</td>
<td>1.4-1.9</td>
<td>Canada</td>
</tr>
<tr>
<td>Ardeparin (Normiflo)</td>
<td>Peroxidative depolymerization</td>
<td>6000</td>
<td>1.9:1</td>
<td>3.0</td>
<td>United States</td>
</tr>
<tr>
<td>Nadroparin (Fraxiparine)</td>
<td>Nitrous acid depolymerization</td>
<td>4500</td>
<td>3.6:1</td>
<td>2.2-3.5</td>
<td>Canada</td>
</tr>
</tbody>
</table>

*Based on plasma antifactor Xa activity.

Table 1. Characteristics of Available Low-Molecular-Weight Heparins (LMWHs)29-31

<table>
<thead>
<tr>
<th>Drug Characteristic</th>
<th>UFH</th>
<th>LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean molecular weight (range), d</td>
<td>15 000 (5000-30 000)</td>
<td>4500 (3000-6000)</td>
</tr>
<tr>
<td>Anti-Xa/Anti-lla ratio</td>
<td>1:1</td>
<td>2:1-4:1</td>
</tr>
<tr>
<td>Bioavailability, %</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>Peak onset, min</td>
<td>20-30</td>
<td>4-6 h</td>
</tr>
<tr>
<td>Plasma half-life, min</td>
<td>60-150</td>
<td>3-6 h</td>
</tr>
<tr>
<td>Elimination</td>
<td>Reticuloendothelial and renal systems</td>
<td>Renal system</td>
</tr>
</tbody>
</table>
The bioavailability of LMWHs after SC injection is approximately 90% compared with 30% for UFH. This difference may be explained by the lower binding affinity of LMWHs for plasma proteins such as histidine-rich glycoproteins, fibronectin, and platelet factor 4. This lower rate of protein binding of LMWHs compared with UFH explains the more predictable anticoagulant response that can be obtained at a given dose of LMWHs. The half-life of 2 to 4 hours following IV administration and 3 to 6 hours following SC injection is longer than the average 90-minute half-life of UFH. In addition, while UFH is eliminated in 2 phases, LMWHs are eliminated almost entirely by the renal route (Table 2). Overall, the combination of predictable anticoagulant response, high bioavailability, and long half-life of LMWHs means that an adequate and predictable anticoagulant response can be achieved with 1 or 2 daily SC injections at fixed or weight-adjusted doses. In addition, because LMWHs do not affect the aPTT, routine laboratory monitoring to assess the anticoagulant effect is not necessary. Although an antifactor Xa assay is available, it is not routinely used owing to its expense and the lack of a clinically defined therapeutic range.

Treatment with LMWHs in animal models results in less bleeding than UFH treatment. This decreased incidence of bleeding may be explained by the following: (1) LMWHs have a lower affinity for platelets, thus inhibiting their function less than UFH; (2) unlike UFH, LMWHs do not increase microvascular permeability; and (3) because of their lower affinity for endothelial cells, von Willebrand factor, and platelets, LMWHs are less likely to interfere with the prothrombotic interaction between platelets and the vessel wall. As a result of less interaction with platelets, heparin-induced thrombocytopenia is less common with LMWHs than with UFH.

While there is a suggestion that the risk of bleeding is lower with LMWHs than with UFH in certain patient groups, this favorable result does not occur in all studies. The reduction in the risk of bleeding observed in early experimental animal models has not been as obvious in clinical studies. Results from clinical trials and meta-analyses show a similar or lower incidence of bleeding with LMWHs; however, other studies have shown higher bleeding rates with LMWHs. Evidence from recent clinical trials indicates that the risk of major bleeding complications with LMWHs is similar to that of UFH; however, minor bleeding complications have been higher in the LMWH trials primarily as a result of injection-site ecchymosis. Overall, it seems that the theoretical advantage of reduced bleeding complications with LMWHs has not been demonstrated clinically, and if anything, the risk of minor bleeding complications is greater than it is with UFH.

Low-molecular-weight heparins are as safe and effective as UFH for the treatment of venous thromboembolism and pulmonary embolism. In addition, they are as safe and effective for prevention of venous thromboembolism following abdominal surgery, orthopedic surgery, spinal surgery, multiple trauma, and other general medical conditions. Trials are currently under way evaluating the role of LMWHs for indications that are currently treated with UFH.

CLINICAL TRIALS IN ACUTE CORONARY SYNDROMES

The efficacy of aspirin in the acute phase of unstable angina has been demonstrated in a number of randomized, controlled clinical trials. The addition of UFH to aspirin may further improve survival and prevent progression to nonfatal myocardial infarction. Oler et al recently conducted a meta-analysis of 6 randomized controlled trials involving 1353 patients comparing aspirin plus UFH with aspirin alone to estimate the effect on subsequent myocardial infarction and death in patients with unstable angina. At 30 days, the addition of UFH to aspirin was associated with a 33% reduction in death or myocardial infarction, or 10.4% in the aspirin group and 7.9% in the aspirin plus UFH group (P = .06).

However, the confidence interval was wide, and included a 56% reduction as well as a 2% excess of events. These statistically marginal benefits may have been a result of limitations of UFH rather than the lack of importance of thrombin inhibition in reducing ischemic events. The limited number of patients studied may also have affected the results.

To identify and evaluate the use of LMWHs in the management of acute coronary syndromes, we conducted a qualitative systematic review of the English-language literature from 1966 to December 1998 using MEDLINE. Key terms used in the literature search included unstable angina, myocardial infarction, heparin, and low-molecular-weight heparin. In addition, the references from relevant literature were reviewed to collect reports not identified in the MEDLINE search. Finally, we contacted experts in the field to obtain information on unpublished results and conference abstracts. We included all controlled clinical trials using LMWHs in unstable angina or non-Q-wave myocardial infarction that reported either efficacy or safety outcomes. All trials were evaluated independently by each of us for inclusion in the review as well as for scientific validity.

There have been 6 prospective, randomized, controlled clinical trials and 1 open-labeled doseranging study completed evaluating the role of LMWHs in patients with unstable angina and non–Q-wave myocardial infarction (Table 3). Gurfinkel et al randomized 219 patients with unstable angina to receive 214 U of nadroparin by SC injection twice daily or 5000 U of UFH by IV bolus followed by a continuous infusion or matching placebo for 5 to 7 days (Table 3). There was a significant reduction in the number of patients reaching the primary end point of recurrent angina, nonfatal myocardial infarction, urgent revascularization, or death in the nadroparin group compared with the UFH and placebo groups, respectively (Table 4). Patients receiving nadroparin had signifi-
cantly less recurrent angina than the patients in the UFH or placebo groups. There was no significant difference in major bleeding complications (Figure 1); however, more patients in the UFH group experienced minor bleeding (Figure 2). There was a trend toward favorable results using nadroparin to prevent myocardial infarction and the need for revascularization, but the sample size was insufficient to conclusively evaluate this end point.

The Fragmin during Instability in Coronary Artery Disease (FRISC) Study Group evaluated the use of dalteparin in 1506 patients with unstable angina or non–Q-wave myocardial infarction (Table 3). Patients presenting within 72 hours of the onset of chest pain were randomized to receive 120 U/kg of dalteparin by SC injection twice daily for 6 days followed by 7500 U subcutaneously once daily for an additional 35 to 45 days or matching placebo. Results after 6 days indicated a 63% reduction in the primary end point of death or myocardial infarction in the dalteparin group compared with the placebo group (Table 4). The absolute risk reduction of 3% correlates to 1 death or myocardial infarction prevented at 6 days for every 34 dalteparin-treated patients. The difference between the 2 groups was not significant when evaluated at 40 and 150 days. The dalteparin-treated groups experienced more minor bleeding complications (Figure 2). The results of the acute phase of this trial are similar to trials conducted comparing UFH with placebo. Therefore, it appears that dalteparin is more effective than placebo in patients with unstable angina or non–Q-wave myocardial infarction. However, long-term benefits of dalteparin were not established in this trial.

The Fragmin in Unstable Coronary Artery Disease Study (FRIC) was a prospective, 2-phase trial in 1482 patients with unstable angina or non–Q-wave myocardial infarction (Table 3). During the acute phase, patients were randomized within 72 hours of the onset of chest pain in an open-labeled fashion to receive 120 U/kg of dalteparin by SC injection twice daily or 5000 U of UFH by IV bolus followed by a continuous infusion. After treatment of the acute condition, patients were randomized into a chronic phase group in a double-blinded manner.

Table 3. Clinical Trials of Low-Molecular-Weight Heparins in Patients With Unstable Angina or Non–Q-Wave Myocardial Infarction

<table>
<thead>
<tr>
<th>Trial (No. of Patients)</th>
<th>Characteristic(s)</th>
<th>Treatment</th>
<th>Control</th>
<th>Primary End Point(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gurfinkel et al* (n = 219)</td>
<td>Unstable angina</td>
<td>Nadroparin, 214 U/kg, SC BID for 5-7 d (n = 68) vs heparin, 5000 U, IV bolus followed by 400 U/kg/d to keep aPTT 2 × baseline for 5-7 d (n = 70) vs placebo for 5-7 d (n = 73)</td>
<td>UFH/placebo</td>
<td>Total events at 7 d; recurrent angina at 7 d; acute MI at 7 d; revascularization at 7 d; death at 7 d</td>
</tr>
<tr>
<td>FRISC (n = 1506)</td>
<td>Unstable angina</td>
<td>Dalteparin, 120 U/kg, SC BID for 6 d followed by 7500 U SC daily for 35-45 d (n = 760) vs placebo (n = 746)</td>
<td>Placebo</td>
<td>Death/MI at 6 d</td>
</tr>
<tr>
<td>FRIC (n = 1482)</td>
<td>Unstable angina</td>
<td>Dalteparin, 120 U/kg, SC BID on days 1-6 (acute phase) (n = 751) followed by 7500 U SC daily on days 6-45 (chronic phase) (n = 567) vs heparin, 5000 U, IV bolus followed by 1000 U/h to keep aPTT 1.5 × baseline on days 1-6 (n = 731) followed by placebo on days 6-45 (n = 565)</td>
<td>UFH</td>
<td>Death/MI/angina at 6-45 d</td>
</tr>
<tr>
<td>TIMI 11A (n = 630)</td>
<td>Unstable angina</td>
<td>Enoxaparin, 1.0 mg/kg, SC BID (n = 399) vs enoxaparin, 1.25 mg/kg, SC BID (n = 321) (in the hospital for at least 48 h followed by 40-60 mg SC BID on discharge to complete 14 d of therapy)</td>
<td>Open label</td>
<td>Major hemorrhage at 14 d</td>
</tr>
<tr>
<td>ESSENCE (n = 3171)</td>
<td>Unstable angina</td>
<td>Enoxaparin, 1.0 mg/kg, SC BID (n = 1607) vs heparin, 5000 U, IV bolus followed by infusion to keep aPTT at 55-85 s (n = 1564)</td>
<td>UFH</td>
<td>Death/MI/angina at 14 d</td>
</tr>
<tr>
<td>TIMI 11B (n = 3910)</td>
<td>Unstable angina</td>
<td>Enoxaparin 30 mg IV bolus then 1.0 mg/kg SC BID for at least 72 h and up to 8 d (acute phase) (n = 1936) followed by 40-60 mg SC BID to complete 43 d of treatment (chronic phase) (n = 1937) vs heparin 70 U/kg IV bolus followed by 15 U/kg per hour infusion to keep aPTT 1.5-2.5 × baseline for at least 72 h (n = 1936) followed by placebo to complete 43 d of treatment (n = 1185)</td>
<td>UFH</td>
<td>Death/MI/urgent revascularization at 8 d</td>
</tr>
<tr>
<td>FRAXIS (n = 3468)</td>
<td>Unstable angina</td>
<td>Nadroparin 0.1 mL/10 kg SC BID for 6 d (n = 1166) vs nadroparin 0.1 mL/10 kg SC BID for 14 d (n = 1151) vs heparin IV bolus followed by infusion for 6 d (n = 1151)</td>
<td>UFH</td>
<td>Cardiovascular death/MI/ refractory angina at 14 d</td>
</tr>
</tbody>
</table>

*All patients received aspirin as well as antianginal therapy (β-blockers, calcium channel blockers, or nitrates) alone or in combination. SC indicates subcutaneously; BID, twice daily; IV, intravenous; aPTT, activated partial thromboplastin time; UFH, unfractionated heparin; MI, myocardial infarction; FRISC, Fragmin during Instability in Coronary Artery Disease Study; FRIC, Fragmin in Unstable Coronary Artery Disease Study; TIMI, Thrombolysis in Acute Myocardial Infarction Study; ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events Study; and FRAXIS, Fraxiparine in Ischemic Syndromes Trial.
to receive 7500 U of dalteparin by SC injection daily or matching placebo on days 6 through 45. Between days 6 and 45 the proportion of patients reaching the primary end point of death, nonfatal myocardial infarction, or recurrent angina was 12.3% in both the dalteparin and UFH groups (Table 4). At 6 days, there was no significant difference between the 2 groups in reaching the same composite triple end point. The proportion of revascularizations at 45 days did not differ between the 2 groups. There was no difference in major and minor bleeding complications between the 2 groups (Figures 1 and 2). The authors concluded that dalteparin seemed to be equivalent to UFH in the acute phase of unstable angina or non–Q-wave myocardial infarction, and that prolonged administration of a reduced dose of dalteparin offered no advantage over long-term therapy with aspirin alone. The trial was not powered to detect a difference in death, myocardial infarction, or recurrent angina during the acute phase.

The Thrombolysis in Acute Myocardial Infarction (TIMI) 11A Trial investigators74 conducted an open-labeled, dose-ranging study using enoxaparin in patients with unstable angina and non–Q-wave myocardial infarction (Table 3). During the acute phase, patients were treated with 1.0 mg/kg of enoxaparin by SC injection twice daily or 1.25 mg/kg of enoxaparin by SC injection twice daily for a minimum of 48 hours. After the acute treatment, patients were discharged and received 40 to 60 mg of enoxaparin by SC injection twice daily to complete 14 days of therapy. The primary end point was major hemorrhage occurring within 2 weeks of enrollment, which occurred more frequently in patients receiving 1.25 mg/kg of enoxaparin than in the 1.0-mg/kg group (Figure 1). No difference was found in any of the secondary end points of death, myocardial infarction, or recurrent ischemia requiring revascularization (Table 4). Since this trial was an unblinded dose-ranging study, no definitive conclusions could be made about the efficacy of enoxaparin in unstable angina.

The Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events Study Group (ESSENCE)57 conducted one of the largest trials comparing the use of LMWHs to UFH in acute coronary syndromes (Table 3). This trial enrolled 3171 patients with unstable angina or non–Q-wave myocardial infarction. Patients were randomized to receive 1.0 mg/kg of enoxaparin subcutaneously twice daily or 5000 U of UFH by IV bolus followed by a continuous infusion.

<table>
<thead>
<tr>
<th>Trial</th>
<th>End Points</th>
<th>LMWH</th>
<th>Control</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gurfinkel et al71</td>
<td>Total events at 7 d‡</td>
<td>Nadroparin</td>
<td>Heparin</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Recurrent angina at 7 d</td>
<td>15 (22)</td>
<td>44 (63)</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td>Acute MI at 7 d</td>
<td>12 (21)</td>
<td>31 (44)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Revascularization at 7 d</td>
<td>0 (0)</td>
<td>4 (6)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Death at 7 d</td>
<td>1 (1.5)</td>
<td>7 (10)</td>
<td>NS</td>
</tr>
<tr>
<td>FRISC72</td>
<td>Death/MI at 6 d‡</td>
<td>Dalteparin</td>
<td>Placebo</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>Death/MI at 40 d</td>
<td>13 (1.8)</td>
<td>36 (4.8)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Death/MI at 150 d</td>
<td>102 (14.0)</td>
<td>116 (15.5)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Revascularization at 150 d</td>
<td>229 (32.9)</td>
<td>254 (35.5)</td>
<td>NS</td>
</tr>
<tr>
<td>FRIC73</td>
<td>Death/MI/angina at 6-45 d‡</td>
<td>Dalteparin</td>
<td>Heparin</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Death/MI/angina at 8 d</td>
<td>69 (12.3)</td>
<td>69 (12.3)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Revascularization at 6-45 d</td>
<td>69 (9.3)</td>
<td>55 (7.6)</td>
<td>NS</td>
</tr>
<tr>
<td>TIMI 11A74</td>
<td>Death at 14 d</td>
<td>Enoxaparin, 1.25 mg/kg</td>
<td>Enoxaparin, 1.0 mg/kg</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>MI at 14 d</td>
<td>7 (2.2)</td>
<td>2 (0.6)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Recurrent ischemia at 14 d</td>
<td>7 (2.2)</td>
<td>9 (2.9)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>14 d‡</td>
<td>Enoxaparin</td>
<td>Heparin</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>48 h</td>
<td>266 (16.6)</td>
<td>309 (19.8)</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>30 d</td>
<td>99 (5.2)</td>
<td>115 (7.4)</td>
<td>NS</td>
</tr>
<tr>
<td>ESSENCE57</td>
<td>Death/MI/angina</td>
<td>318 (19.8)</td>
<td>364 (23.3)</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>14 d‡</td>
<td>Enoxaparin</td>
<td>Heparin</td>
<td>.048</td>
</tr>
<tr>
<td></td>
<td>43 d</td>
<td>240 (12.4)</td>
<td>281 (14.5)</td>
<td>.029</td>
</tr>
<tr>
<td>TIMI 11B77</td>
<td>Death/MI/urgent revascularization</td>
<td>275 (14.2)</td>
<td>324 (16.7)</td>
<td>.048</td>
</tr>
<tr>
<td></td>
<td>43 d</td>
<td>335 (17.3)</td>
<td>382 (19.7)</td>
<td>.048</td>
</tr>
</tbody>
</table>

*LMWH indicates low-molecular-weight heparin; MI, myocardial infarction; NS, not significant; FRISC, Fragmin during Instability in Coronary Artery Disease Study; FRIC, Fragmin in Unstable Coronary Artery Disease Study; TIMI, Thrombolysis in Acute Myocardial Infarction Study; and ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events Study.
†Data are given as number (percentage) of events.
‡Primary end point.
Treatment continued for a period of at least 48 hours and for as long as 8 days. At the conclusion of the trial, significantly fewer enoxaparin-treated patients reached the primary end point of death, nonfatal myocardial infarction, or recurrent angina at 14 days (Table 4). This significant difference was maintained at 30 days. There was no difference between groups at 48 hours, nor was there a difference in the combination end point of death or myocardial infarction at 14 and 30 days. Results after 1 year of follow-up have been presented, and the early benefit of enoxaparin in the primary end point was maintained (32% for enoxaparin vs 35.7% for UFH; \( P = .02 \)).\(^{37}\) The difference between the 2 groups was primarily the result of less recurrent angina in the enoxaparin group, which composed 75% of events. There was no difference between groups in major bleeding complications (Figure 1); however, more patients in the enoxaparin groups experienced minor bleeding (Figure 2). One limitation of this trial was the fixed rather than weight-adjusted UFH nomogram. Only 46% of patients had therapeutic levels of UFH at 24 hours, which improved to only 51.3% at 48 hours. Although a weight-adjusted heparin nomogram may achieve a therapeutic aPTT more rapidly in patients with venous thromboembolism, the importance of weight-adjusted nomograms in patients with angina has not been thoroughly studied.\(^{79,80}\)

The Thrombolysis in Myocardial Infarction (TIMI) 11B Trial investigators\(^{75}\) conducted a second study comparing 1.0 mg/kg of enoxaparin by SC injection twice daily with UFH using a weight-adjusted UFH nomogram for the treatment of unstable angina and non-Q-wave myocardial infarction (Table 3). During the acute phase, patients received treatment for a minimum of 72 hours and up to 8 days. Following acute treatment, patients initially randomized to enoxaparin continued to receive enoxaparin for an additional 35 days at a weight-adjusted reduced dose of 40 to 60 mg SC twice daily. Patients randomized to UFH received placebo during the chronic phase. Results were presented at the 71st Scientific Sessions of the American Heart Association in Dallas, Tex, and indicate that fewer enoxaparin-treated patients reached the primary end points of death, nonfatal myocardial infarction, and severe recurrent ischemia requiring revascularization during the acute phase (Table 4).\(^{77}\) This initial benefit was maintained at 43 days; however, no relative reduction in events occurred during the chronic phase. Superiority of enoxaparin in the acute phase was not associated with any increase in major bleeding (Figure

**Table 1.** Major bleeding complications. Gurfinkel et al\(^{71}\) indicate a fall in hemoglobin level of more than 20 g/L (>2 g/dL), a need for transfusion, or both; the Framingham during Instability in Coronary Artery Disease Study (FRISC),\(^ {72}\) a fall in hemoglobin level of more than 20 g/L (>2 g/dL) associated with signs and symptoms, intracranial bleeding, or bleeding leading to transfusion, interruption of treatment, or death; the Framingham in Unstable Coronary Artery Disease Study (FRIC),\(^ {73}\) a fall in hemoglobin level of more than 20 g/L (>2 g/dL), a required transfusion, intracranial hemorrhage, or death or cessation of therapy; the Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events Study (ESSENCE),\(^ {57}\) a fall in hemoglobin level of more than 30 g/L (>3 g/dL), bleeding resulting in death, transfusion of at least 2 U of blood, or a retroperitoneal, intracranial, or intraocular hemorrhage; and the Thrombolysis in Myocardial Infarction (TIMI) 11B Trial in- vestigators\(^ {76}\) conducted a second study comparing 1.0 mg/kg of enoxaparin by SC injection twice daily with UFH using a weight-adjusted UFH nomogram for the treatment of unstable angina and non–Q-wave myocardial infarction (Table 3). During the acute phase, patients received treatment for a minimum of 72 hours and up to 8 days. Following acute treatment, patients initially randomized to enoxaparin continued to receive enoxaparin for an additional 35 days at a weight-adjusted reduced dose of 40 to 60 mg SC twice daily. Patients randomized to UFH received placebo during the chronic phase. Results were presented at the 71st Scientific Sessions of the American Heart Association in Dallas, Tex, and indicate that fewer enoxaparin-treated patients reached the primary end points of death, nonfatal myocardial infarction, and severe recurrent ischemia requiring revascularization during the acute phase (Table 4).\(^ {77}\) This initial benefit was maintained at 43 days; however, no relative reduction in events occurred during the chronic phase. Superiority of enoxaparin in the acute phase was not associated with any increase in major bleeding (Figure

![Figure 1. Major bleeding complications. Gurfinkel et al\(^ {71}\) indicate a fall in hemoglobin level of more than 20 g/L (>2 g/dL), a need for transfusion, or both; the Framingham during Instability in Coronary Artery Disease Study (FRISC),\(^ {72}\) a fall in hemoglobin level of more than 20 g/L (>2 g/dL) associated with signs and symptoms, intracranial bleeding, or bleeding leading to transfusion, interruption of treatment, or death; the Framingham in Unstable Coronary Artery Disease Study (FRIC),\(^ {73}\) a fall in hemoglobin level of more than 20 g/L (>2 g/dL), a required transfusion, intracranial hemorrhage, or death or cessation of therapy; the Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events Study (ESSENCE),\(^ {57}\) a fall in hemoglobin level of more than 30 g/L (>3 g/dL), bleeding resulting in death, transfusion of at least 2 U of blood, or a retroperitoneal, intracranial, or intraocular hemorrhage; and the Thrombolysis in Myocardial Infarction (TIMI) 11B Trial investigators\(^ {76}\) conducted a second study comparing 1.0 mg/kg of enoxaparin by SC injection twice daily with UFH using a weight-adjusted UFH nomogram for the treatment of unstable angina and non–Q-wave myocardial infarction (Table 3). During the acute phase, patients received treatment for a minimum of 72 hours and up to 8 days. Following acute treatment, patients initially randomized to enoxaparin continued to receive enoxaparin for an additional 35 days at a weight-adjusted reduced dose of 40 to 60 mg SC twice daily. Patients randomized to UFH received placebo during the chronic phase. Results were presented at the 71st Scientific Sessions of the American Heart Association in Dallas, Tex, and indicate that fewer enoxaparin-treated patients reached the primary end points of death, nonfatal myocardial infarction, and severe recurrent ischemia requiring revascularization during the acute phase (Table 4).\(^ {77}\) This initial benefit was maintained at 43 days; however, no relative reduction in events occurred during the chronic phase. Superiority of enoxaparin in the acute phase was not associated with any increase in major bleeding (Figure

![Figure 2. Minor bleeding complications. LMWH indicates low-molecular-weight heparin; UFH, unfractionated heparin; FRISC, Framingham during Instability in Coronary Artery Disease Study; FRIC, Framingham in Unstable Coronary Artery Disease Study; ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events Study; asterisk, \( P = .01 \); and dagger, \( P < .001 \).](https://archinte.jamanetwork.com/)

©1999 American Medical Association. All rights reserved.
3).76 This trial enrolled 3468 patients presenting with either unstable angina or non–Q-wave myocardial infarction. Patients were randomized to receive 1 of 3 treatments: 0.1 mL/10 kg of nadroparin by SC injection every 12 hours for 6 days; 0.1 mL/10 kg of nadroparin by SC injection every 12 hours for 14 days; or UFH for 6 days. Results indicated no significant difference in the primary end point between the 3 treatment groups for cardiovascular death, myocardial infarction, or refractory or recurrent angina at 14 days, with event rates of 17.8%, 20.0%, and 18.1%, respectively. Major bleeding was similar between the groups when evaluated at 6 days; however, a higher major bleeding rate occurred in the 14-day nadroparin arm compared with the 6-day nadroparin and UFH groups (3.5%, 1.5%, and 1.6%, respectively) when evaluated at 14 days.

PHARMACOECONOMICS

The positive clinical results demonstrated in the ESSENCE trial were supplemented with a pharmacoeconomic analysis comparing LMWHs and UFH in acute coronary syndromes. Mark et al81 conducted a prospective economic assessment of 936 patients enrolled in the ESSENCE trial. These patients represented 85% of all the patients enrolled from the United States. Results of the cost analysis demonstrated that the improved clinical outcomes for patients treated with enoxaparin were associated with a cost saving. Despite the US $75 incremental drug cost of administering enoxaparin rather than UFH, cost savings of US $763 were realized at hospital discharge and US $1172 at 30 days. The most substantial resource effect of enoxaparin was a reduction in the use of coronary angioplasty, which was a result of the clinical reduction of recurrent ischemic events. Additional savings resulted from the estimated reduction in the cost of IV therapy, tubing and appliances, and aPTT monitoring. This analysis did not evaluate cost of outpatient care or indirect costs related to lost productivity. The authors concluded that the clinical as well as economic advantages of using enoxaparin over UFH made it a dominant strategy in the management of acute coronary syndromes.

A Canadian cost-effectiveness analysis has also been conducted based on the 30-day end point of the ESSENCE trial.82 Based on costs of medical care in Canada, the average cost per patient for enoxaparin was determined to be Can $848 vs Can $892 for UFH. (At the time of this analysis, Can $1.00 was equivalent to US $0.66.) As with the US economic analysis, enoxaparin was considered the dominant antithrombotic pharmacotherapeutic strategy for patients with unstable coronary artery disease.

CONCLUSIONS

The data evaluating the use of LMWHs in the management of acute coronary syndromes continue to accumulate. Despite the encouraging clinical trial results, the variation in study designs and trial end points complicates a quantitative systematic comparison of all these data. However, evidence from TIMI 11B and ESSENCE involving over 7000 patients is sufficient to allow recommending the use of LMWHs in the management of acute coronary syndromes.

Low-molecular-weight heparins are superior to placebo and UFH in reducing ischemic events or death in the acute phase of unstable angina or non–Q-wave myocardial infarction. Prolonged therapy with lower doses of LMWHs may not offer any advantage over aspirin in the prevention of coronary events or death. Major bleeding complications are similar for LMWHs and UFH, but minor bleeding complications are more common with LMWHs primarily because of injection-site hematomas. Finally, LMWHs appear to be cost-effective compared with UFH based on pharmacoeconomic analyses conducted in Canada and the United States based on the ESSENCE study results. Taken together, the use of LMWHs for the treatment of unstable angina or non–Q-wave myocardial infarction should be favored over UFH.

Several questions regarding LMWHs remain unresolved. First, are all LMWH agents comparable? Although the biochemical distinctions between agents may be minor, few data define whether important clinical differences between agents result. Evidence from FRAXIS and FRAXIS failed to demonstrate increased efficacy of LMWHs over UFH by using dalteparin and nadroparin, respectively.83,84 As a result, the effective dose of these agents remains uncertain. Alternatively, data from ESSENCE and TIMI 11B show the greatest benefits and demonstrate superiority of UFH using enoxaparin.85,86 Thus, based on the best available evidence, a class effect of LMWH preparations should not be assumed, and enoxaparin should be the preferred LMWH agent for patients with unstable angina or non–Q-wave myocardial infarction. Enoxaparin, 1.0 mg/kg, subcutaneously twice daily should be continued for at least 72 hours, but not beyond the hospital phase.

Other unanswered questions include the use of LMWHs with other antiplatelet agents such as the IV and oral glycoprotein IIb/IIIa receptor antagonists or direct thrombin inhibitors. Results of large, randomized, controlled trials using glycoprotein IIb/IIIa receptor antagonists for acute coronary syndromes are encouraging.87-89 Unfortunately, it may be many years before these agents are evaluated in combination with LMWHs. To date, clinical experience with direct
thrombin inhibitors has been dis-
appointing, with no clear evidence of clinical efficacy and potential in-
creased bleeding risk.87,88 Promis-
sing results from the Organisation to Assess Strategies for Ischemic Synd-
dromes (OASIS-2) Investigators
demonstrated an improved out-
come compared with UFH; how-
vsoever, the benefit in combination with
versus aspirin: primary end point analyses from the ATACs trial.
6. Neri Serneri GG, Modesti PA, Gensini GF, et al. Randomized,
cross-over study of low-molecular
weight heparins and aspirin in un-
myocardial infarction during the acute phase of
unstable angina. Circulation. 1993;88:2045-
2048.
antithrombotic therapy in unstable rest angina and
non-Q-wave infarction in patients taking aspirin users:
9. Research will
continue in an attempt to improve
outcomes for patients with cardio-
vascular disease. In the meantime,
LMWHs appear to be a major advance
in the management of unstable angina and non-Q-wave myo-
cardial infarction.
Accepted for publication January 26, 1999.
Dr Tisdale has received lecture honoraria from Hoechst-Marion Roussel Inc, Kansas City, Mo; Wyeth-
Ayerst Laboratories, Cranbury, NJ; Merck & Co, Whitehouse Station, NJ; Boehringer-Mannheim, now merged
with Roche Pharmaceuticals, Nutley, NJ; and G. D. Searle & Co, Shikie, Ill. He has received research grants from
Hoechst-Marion Roussel Inc and Merck & Co. He has been a consultant
for Hoechst-Marion Roussel Inc; Wyeth-Ayerst Laboratories; Rhone-
Poulenc-Rorer Pharmaceuticals, Collegeville, Pa; Roche Pharmacueticals,
Parke-Davis, Morris Plains, NJ; Cor Therapeutics, San Francisco,
Calif; and 3M Pharmaceuticals, St Paul, Minn. Dr Borzak has served on the speakers’ bureau and received
grants from Rhone-Poulenc-Rorer.
Corresponding author: Peter J.
Zed, PharmD, CSU Pharmaceutical Sciences,
Vancouver Hospital and Health Sciences Center, 855 W 12th Ave, Van-
couver, British Columbia, Canada, V5Z 1M9 (e-mail: zed@interchange.ubc.ca).

REFERENCES
1. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the
2. Theroux P, Quinette H, McCans J, et al. Aspirin, hepa-
in, or both to treat acute unstable angina. N Engl J Med.
3. The RISC Group. Risk of myocardial infarction and death during treatment with low-dose aspirin and
intravenous heparin in men with unstable coro-

ARCH INTERN MED/VOL 159, SEP 13, 1999
1836
©1999 American Medical Association. All rights reserved.
53. Bergqvist D, Burmark US, Frisell J, et al. Throm-
54. Bergqvist D, Burmark US, Frisell J, et al. Prospec-
52. Hull RD, Raskob GE, Pineo GF, et al. Subcutane-
61. Turpie AGG, Levine MN, Hirsch J, et al. A ran-
49. Anderson DR, O'Brien BJ, Levine MN, Roberts R,
61. Turpie AGG, Levine MN, Hirsch J, et al. A ran-
heparin in the treatment of patients with
acute venous thromboembolism: results of a meta-
47. Siragusa S, Cosmi B, Piovella F, Hirsh J, Güns-
berg JS. Low molecular-weight heparin and unfractionated
heparin in the treatment of patients with
acute venous thromboembolism: a meta-
48. Lensing AWA, Prins MH, Davidson BL, Hirsch J.
Treatment of deep-vein thrombosis with low mo-
olecular-weight heparins: a meta-analysis. Arch
49. Anderson DR, O'Brien BJ, Levine MN, Roberts R,
Wells PS, Hirsh J. Efficacy and cost of low-
molecular-weight heparin compared with stan-
dard heparin for the prevention of deep-vein throm-
1993;119:1105-1112.
50. Lassen MR, Boris UC, Christiansen HM, et al. Cli-
tical trials with low molecular weight heparins in
the prevention of postoperative thromboembolic
complications: a meta-analysis. Semin Thromb
51. Nuromohamed MT, Rosendaal FR, Buller HR, et al.
Low molecular-weight heparin versus stan-
dard heparin in general and orthopedic surgery:
52. Hull RD, Raskold GE, Pineo GF, et al. Subcutane-
ous low molecular weight heparin compared with
continuous intravenous heparin in the treatment
326:975-982.
53. Bergqvist D, Burmark US, Frisell J, et al. Throm-
boprophylactic effect of low molecular weight heparin
started in the evening before elective gen-
low molecular weight heparin administered pri-
marily at home with unfractionated heparin in the
hospital for proximal deep vein thrombosis. N Engl J
ment of venous thrombosis with intravenous un-
fractionated heparin administered in the hospital as
a continuous subcutaneous low molecular-
weight heparin administered at home. N Engl J
parison of low-molecular weight heparin with unfractionated
heparin for unstable coronary artery
57. The Columbus Investigators. Low molecular-
weight heparin in the treatment of patients with
337:657-662.
parison of low molecular weight heparin with
unfractionated heparin for acute pulmonary embo-
59. Kakker W, Cohen AT, Edmonson RA, et al. Low mo-
lculeweight heparin versus standard heparin for prevent-
ion of venous thromboembolism after ma-
60. Turpie AGS, Levine MN, Hirsh J, et al. A ran-
domized controlled trial of a low molecular weight
heparin (enoxaparin) to prevent deep-vein throm-
51. Nuromohamed MT, Rosendaal FR, Buller HR, et al.
Low molecular-weight heparin versus stan-
dard heparin in general and orthopedic surgery:
52. Hull RD, Raskold GE, Pineo GF, et al. Subcutane-
ous low molecular weight heparin compared with
continuous intravenous heparin in the treatment
326:975-982.
53. Bergqvist D, Burmark US, Frisell J, et al. Throm-
boprophylactic effect of low molecular weight heparin
started in the evening before elective gen-