Low-Molecular-Weight Heparin
A Review of the Results of Recent Studies of the Treatment of Venous Thromboembolism and Unstable Angina

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Low-molecular-weight heparins (LMWHs) are a new class of anticoagulants derived from unfractionated heparin (UFH). They have a number of advantages over UFH that have led to their increasing use for a number of thromboembolic indications.1 This article will review the limitations of UFH and the mechanisms by which LMWHs overcome these limitations and discuss the results of recent clinical trials evaluating LMWHs for the treatment of venous thrombosis, pulmonary embolism, and unstable angina.

Limitations of UFH
Heparin has pharmacokinetic, biophysical, and biological limitations.2 LMWHs overcome the pharmacokinetic and some of the biological limitations of UFH, but they share the same biophysical limitations.

Pharmacokinetic Limitations of UFH
The pharmacokinetic limitations of heparin are caused by its nonspecific binding to proteins and cells.2,3 Because heparin is highly negatively charged, it binds in a pentasaccharide-independent fashion to a variety of plasma proteins (including histidine-rich glycoprotein, vitronectin, lipoproteins, fibronectin, and fibrinogen) and to proteins secreted by platelets (platelet factor 4 [PF4] and high-molecular-weight von Willebrand factor) and endothelial cells (high-molecular-weight von Willebrand factor).2 Some heparin-binding proteins are acute-phase reactants, the levels of which are elevated in sick patients.4 In addition, during the clotting process, PF4 and von Willebrand factor are released from platelets and endothelial cells, respectively.

The variability in plasma levels of heparin-binding proteins in patients with thromboembolic diseases4 is responsible for both the unpredictable anticoagulant response to UFH4 and the very high heparin requirements in some of these patients (heparin resistance).5

Biophysical Limitations
The biophysical limitations of heparin reflect the inability of the heparin-antithrombin complex to inactivate thrombin-bound to fibrin5 and factor Xa bound to phospholipid surfaces within the prothrombinase complex.6 The inability of heparin to inactivate surface-bound thrombin and factor Xa may explain why heparin is of only limited efficacy in unstable angina, high-risk coronary angioplasty, and coronary thrombolysis.

Biological Limitations
Apart from the well-known complication of bleeding, which is common to all anticoagulants, UFH can produce thrombocytopenia and osteoporosis.

Thrombocytopenia
Heparin binds to platelets, causing activation6 and release of PF4. Heparin complexes PF4 and stimulates the formation of antibodies that cause heparin-induced thrombocytopenia (HIT).7 The reported incidence of HIT varies widely, but in a recent large randomized trial,8 it was ≈3%. Thrombocytopenia usually begins between 5 and 15 days after heparin is begun (median, 10 days)11 but can occur within hours in patients who have been previously exposed to heparin.11 The incidence of arterial or venous thrombosis with HIT is unknown but has been estimated to occur in ≈20% of patients with HIT. Thrombosis is thought to be triggered by immune complex–induced platelet activation.

There is evidence from a large randomized trial that the incidences of heparin-associated IgG and of HIT are less in patients treated with prophylactic doses of LMWH than those treated with low-dose UFH.10 However, there are reports that the administration of LMWHs can be associated with the development of thrombocytopenia both in previously unexposed individuals and in those with a history of HIT.12 There is also evidence that LMWH cross-reacts with plasma from patients with recent HIT.13 In contrast to the LMWHs, the heparinoid danaparoid sodium, which is said to be free of contaminating heparin, exhibits minimal cross-reactivity in in vitro assays for HIT13 and has been used successfully in patients with a history of HIT.13,14

Osteoporosis
Osteoporosis is a well-recognized complication of long-term heparin treatment.15–17 Reports from recent clinical studies suggest that 2% to 3% of patients receiving UFH for >3 months develop symptomatic bone fractures and that up to one third have had an asymptomatic reduction in bone density as determined by dual-photon absorptiometry.15–17

In a series of studies, Shaughnessy and associates18 reported that UFH produces a concentration-dependent effect on bone density.

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on various indexes of bone metabolism in rats. Thus, UFH (1) increases bone resorption from cultured fetal calvariae, (2) decreases cancellous bone volume,19 and (3) decreases osteoblast and osteoid surface and increases osteoclast surface in rats. All these effects are heparin chain length–dependent and are less marked with LMWH.18,19

Initial case reports of successful use of LMWH in patients whose treatment with heparin was complicated with symptomatic osteoporosis20–24 have been supported by the results of a small randomized study that showed that the incidence of bone fracture was less in patients assigned LMWH than those assigned UFH.16

**LMWHs**

LMWHs are derived from UFH by chemical or enzymatic depolymerization to yield fragments that are approximately one third the size of heparin. Like UFH, they are heterogeneous with respect to molecular size and anticoagulant activity. LMWHs have a mean molecular weight of 4000 to 5000, with a molecular weight distribution of 1000 to 10 000. Depolymerization of UFH into lower-molecular-weight fragments results in 5 main changes in its properties; all are due to reduced binding of LMWH to proteins or cells (Table 1).

Compared with UFH, LMWHs have (1) reduced ability to catalyze inactivation of thrombin because the smaller fragments cannot bind to thrombin but retain their ability to inactivate factor Xa;21–24 (2) reduced nonspecific binding to plasma proteins, with a corresponding improvement in the predictability of their dose-response relationship;25 (3) reduced binding to macrophages and endothelial cells, with an associated increase in their plasma half-life; (4) reduced binding to platelets and PF4, which may explain the lower incidence of HIT;26; and (5) possibly reduced binding to osteoblasts, which results in less activation of osteoclasts and an associated reduction in bone loss (Table 1). LMWHs are cleared principally by the renal route, and their biological half-life is increased in patients with renal failure.26–28

The LMWHs approved for use in Europe, Canada, and the United States are shown in Table 2. Because some of these LMWHs are prepared by different methods of depolymerization and differ to some extent in their pharmacokinetic properties and anticoagulant profiles, they may not be clinically interchangeable.

**Anticoagulant Effects of LMWHs**

Like UFH, LMWHs produce their major anticoagulant effect by activating antithrombin (AT). Their interaction with AT is mediated by a unique pentasaccharide sequence found on fewer than one third of LMWH molecules. Because a minimum chain length of 18 saccharides (including the pentasaccharide sequence) is required for ternary complex formation, only the 25% to 50% of LMWH species that are above this critical chain length are able to inactivate thrombin. In contrast, all LMWH chains that contain the high-affinity pentasaccharide catalyze the inactivation of factor Xa. Consequently, commercial LMWHs have ratios of anti-factor Xa to anti-IIa that vary between 4:1 and 2:1, depending on their molecular size distribution (the Figure). In contrast to LMWH, virtually all UFH molecules contain ≥18 saccharide units.31,32 Therefore, UFH has a ratio of anti-factor Xa to anti-factor IIa of 1:1.

**Clinical Experience With LMWH Preparations**

LMWHs have been evaluated in a large number of randomized clinical trials and have been shown to be safe and effective for the prevention and treatment of venous thrombosis. More recently, LMWH preparations have also been evaluated in patients with acute pulmonary embolism and those with unstable angina.

**TABLE 1. Biological Consequences of Reduced Binding of LMWH to Proteins and Cells**

<table>
<thead>
<tr>
<th>Binding Target</th>
<th>Biological Effects</th>
<th>Clinical Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin</td>
<td>Reduced ratio of anti-IIa to anti-Xa</td>
<td>Unknown</td>
</tr>
<tr>
<td>Proteins</td>
<td>More predictable anticoagulant response</td>
<td>Monitoring of anticoagulant effect unnecessary</td>
</tr>
<tr>
<td>Macrophages</td>
<td>Cleared through renal mechanism</td>
<td>Longer plasma half life, once-daily SC treatment effective</td>
</tr>
<tr>
<td>Platelets</td>
<td>Reduced incidence of heparin-dependent antibody</td>
<td>Reduced incidence of heparin-induced thrombocytopenia</td>
</tr>
<tr>
<td>Osteoblasts</td>
<td>Reduced activation of osteoclasts</td>
<td>Lower incidence of osteopenia</td>
</tr>
</tbody>
</table>

**TABLE 2. Comparison of LMWH Preparations**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Method of Preparation</th>
<th>Mean Molecular Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ardeparin (Normiflo)</td>
<td>Peroxidative depolymerization</td>
<td>6000</td>
</tr>
<tr>
<td>Dalteparin (Fragmin)</td>
<td>Nitrous acid depolymerization</td>
<td>6000</td>
</tr>
<tr>
<td>Enoxaparin (Lovenox)</td>
<td>Benzylation and alkaline depolymerization</td>
<td>4200</td>
</tr>
<tr>
<td>Nadroparin (Fraxiparine)</td>
<td>Nitrous acid depolymerization</td>
<td>4500</td>
</tr>
<tr>
<td>Reviparin (Clivarine)</td>
<td>Nitrous acid depolymerization, chromatographic purification</td>
<td>4000</td>
</tr>
<tr>
<td>Tinzaparin (Innohep)</td>
<td>Heparinase digestion</td>
<td>4500</td>
</tr>
</tbody>
</table>

Data from Weitz et al.1 Table used with permission from author.

LMWH activity. Approximately 25% to 50% of LMWH molecules of different commercial preparations contain ≥18 saccharide units; these molecules inhibit both thrombin and factor Xa. Remaining 50% to 75% of LMWH molecules contain ≤18 saccharide units and inhibit only factor Xa.
TREATMENT OF VENOUS THROMBOEMBOLISM

A number of LMWH preparations have been compared with UFH in hospitalized patients in many well-designed studies. The results of studies published up to 1995 have been summarized in a meta-analysis33 (Tables 3 and 4) in which the data for each of the 4 LMWHs have been pooled separately.

The results indicate that all 4 LMWH preparations evaluated are as effective and safe as intravenous UFH and that event rates (recurrent thromboembolism and major bleeding) are low and similar with all the LMWHs. It is noteworthy that the LMWHs were administered by subcutaneous injection in unmonitored weight-adjusted doses, whereas UFH was monitored by the activated partial thromboplastin time (APTT).

The study evaluating Tinzaparin (Innohep)34 stands out because it was double blind and relatively large and used a once-daily dosing regimen (175 anti-Xa units/kg). Major bleeding was less with Tinzaparin than UFH. However, whether the observed difference in bleeding reflects a safety advantage of Tinzaparin or is the result of the unusually high rate of major bleeding in the UFH group (5%) is uncertain. In this context, the study reported by Simmoneau and associates35 comparing the efficacy and safety of Tinzaparin with UFH in acute pulmonary embolism (described in detail below), which used an identical once-daily regimen of Tinzaparin, reported equal efficacy and safety for the Tinzaparin LMWH and UFH.

Since the publication of the pooled analysis, 4 large randomized trials have been completed35–37: 2 of patients with venous thrombosis,36,37 1 of patients with venous thrombosis or pulmonary embolism,38 and 1 of patients with pulmonary embolism.35 The design used in 3 of the studies36–38 capitalized on the more predictable anticoagulant response of LMWH by encouraging patients assigned to LMWH to be treated at home, while those assigned to UFH were treated in the standard manner in hospital with a continuous intravenous infusion.

In the study by Levine and associates,36 eligible patients with proximal vein thrombosis were randomly assigned to intravenous heparin in hospital or a strategy of LMWH (enoxaparin sodium) 1 mg/kg (100 anti-Xa units/kg SC) twice daily administered primarily at home. The design allowed patients assigned LMWH to be treated at home without admission and hospitalized patients to be discharged early. Thirteen of 247 LMWH patients (5.3%) developed recurrent thromboembolism compared with 17 of 253 patients (6.7%) in the heparin group (*P* = 0.57). Five LMWH patients developed major bleeding compared with 3 heparin patients. After randomization, the mean length of hospital stay for the LMWH group was 1.1 days compared with 6.5 days for the heparin group.

In the study by Koopman and associates,37 patients with deep venous thrombosis were randomly assigned to intravenous heparin in hospital (5000 IU as a bolus followed by 1250 U/h) with APTT or LMWH (nadoparame calcium) twice daily subcutaneously with a weight-adjusted dosage regimen. Patients weighing <50 kg received a daily dose of 8200 anti-Xa units; those weighing between 50 and 70 kg received 12ths300 anti-Xa units; and those weighing >70 kg received 18ths400 anti-Xa units. The design allowed outpatients to go home immediately on LMWH and hospitalized patients to be discharged early on LMWH. Fourteen of 202 LMWH patients (6.9%) developed recurrent thromboembolism compared with 17 of 198 patients (8.6%) in the heparin group (*P* > 0.5). One LMWH patient developed major bleeding compared with 4 heparin patients.

A comparison of the results of the studies reported by Levine et al36 and by Koopman et al37 is shown in Table 5. The results are similar and indicate that LMWH administered

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**TABLE 3.** LMWH Versus Heparin in the Treatment of Deep Venous Thrombosis: Symptomatic Recurrent Venous Thromboembolic Complications During Initial Treatment and 3- to 6-Month Follow-Up

<table>
<thead>
<tr>
<th>Agent</th>
<th>Patients, n/total (%)</th>
<th>Relative Risk Reduction (95% CI)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LMWH</td>
<td>Heparin</td>
<td></td>
</tr>
<tr>
<td>Nadroparin (Fraxiparin)</td>
<td>20/361 (5.5)</td>
<td>32/355 (9.0)</td>
<td>40 (−5−66)</td>
</tr>
<tr>
<td>Tinzaparin (Logiparin)</td>
<td>6/213 (2.8)</td>
<td>15/219 (6.9)</td>
<td>59 (−1−83)</td>
</tr>
<tr>
<td>Enoxaparin (Clexane)</td>
<td>13/314 (4.1)</td>
<td>20/320 (6.3)</td>
<td>35 (−32−68)</td>
</tr>
<tr>
<td>Dalteparin (Fragmin)</td>
<td>16/322 (5.0)</td>
<td>8/339 (2.4)</td>
<td>−110 (−374−7)</td>
</tr>
</tbody>
</table>

Data from Kuijer et al.35 Table used with permission from author.

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**TABLE 4.** LMWH Versus Heparin: Incidence of Major Bleeding Complications During Initial Heparin Treatment, Including 48 Hours After Heparin Cessation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Patients, n/total (%)</th>
<th>Relative Risk Reduction (95% CI)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LMWH</td>
<td>Heparin</td>
<td></td>
</tr>
<tr>
<td>Nadroparin (Fraxiparin)</td>
<td>4/446 (0.9)</td>
<td>10/436 (2.3)</td>
<td>59 (−16−86)</td>
</tr>
<tr>
<td>Tinzaparin (Logiparin)</td>
<td>1/213 (0.5)</td>
<td>11/219 (5.0)</td>
<td>91 (&gt;0.01)</td>
</tr>
<tr>
<td>Enoxaparin (Clexane)</td>
<td>5/314 (1.6)</td>
<td>3/320 (0.9)</td>
<td>−70 (−580−58)</td>
</tr>
<tr>
<td>Dalteparin (Fragmin)</td>
<td>2/433 (0.5)</td>
<td>5/464 (1.0)</td>
<td>55 (−99−90)</td>
</tr>
</tbody>
</table>

Data from Kuijer et al.35 Table used with permission from author.
on an out-of-hospital basis in eligible patients with deep venous thrombosis is as effective and safe as intravenous heparin administered in hospital. These findings have the potential to change our current approach to the treatment of venous thrombosis, with improved patient convenience and reduced health care costs.

Both of these studies\textsuperscript{36,37} excluded patients with symptomatic pulmonary embolism or a history of recent previous venous thromboembolism. To address this, both groups collaborated to perform the COLUMBUS study\textsuperscript{38} (Table 6), which was a randomized study of 1021 patients with symptomatic venous thromboembolism. Patients with venous thrombosis or pulmonary embolism were randomly allocated to receive either subcutaneous LMWH (riviparin sodium) or adjusted-dose intravenous UFH. Warfarin was started concomitantly and continued for 3 months. The dosage regimen for LMWH was 6300 anti-Xa units twice daily for patients weighing \(>60\) kg, 4200 anti-Xa units twice daily for persons weighing 46 to 60 kg, and 3500 anti-Xa units twice daily for those weighing 35 to 45 kg. Approximately one third of the patients had associated pulmonary embolism, and most were treated in hospital. Of the patients with venous thrombosis, 27\% were treated out of hospital, and an additional 15\% were discharged during the first 3 days of treatment. As a result, the mean hospital stay was 3 days shorter for patients assigned to LMWH.

Of the 510 patients assigned to LMWH, 5.3\% had recurrent thromboembolic events over the 3 months of treatment compared with 4.9\% of the 511 patients assigned to UFH. Major bleeding occurred in 3.1\% of patients assigned to LMWH compared with 2.3\% assigned to receive UFH \((P=0.63)\). The mortality rates were 7.1\% and 7.6\%, respectively \((P=0.89)\). This study confirms the efficacy and safety of outpatient LMWH for the treatment of patients with acute pulmonary embolism.

The effectiveness and safety of unmonitored subcutaneous LMWH (riviparin) in symptomatic pulmonary embolism reported in the COLUMBUS study were confirmed in a study of 612 patients with symptomatic pulmonary embolism reported by Simonneau and associates,\textsuperscript{35} who used a different LMWH (Tinzaparin). Patients who did not require thrombolytic therapy or pulmonary embolectomy were randomly allocated to receive LMWH (175 anti-Xa units/kg SC once daily) or UFH (50 U/kg bolus followed by a continuous infusion of 500 U \(\cdot\) kg\(^{-1}\) \(\cdot\) d\(^{-1}\) adjusted to obtain an APTT ratio of 2.0 to 3.0).

The outcome measure, a composite of recurrent thromboembolism, major bleeding, and death, was assessed on days 8 and 90. On day 8, 9 of 308 patients (2.9\%) assigned to UFH and 9 of 304 patients (3.0\%) assigned to LMWH reached at least 1 of the primary end points. By day 90, 22 patients (7.1\%) patients to UFH and 18 patients (5.9\%) assigned to LMWH reached 1 of the primary end points \((P=0.54)\) (Table 6). The rate of major bleeding was similar in both groups (2.6\% and 2.0\%, respectively). There were 3 deaths at 8 days and 14 deaths at 90 days (4.5\%) in patients assigned to UFH and 4 deaths at 8 days and 12 deaths at 90 days (3.9\%) in patients assigned to LMWH. Five deaths were treatment related in the UFH group (3 from pulmonary embolism and 2 from major bleeding), and 4 were treatment related in the LMWH group (3 from pulmonary embolism and 1 from bleeding).

The findings of this study, combined with those of the COLUMBUS study, indicate that subcutaneous weight-adjusted LMWH is as effective and safe as intravenous UFH. LMWH, however, is much more convenient.

Most of these studies evaluating LMWH preparations for the treatment of venous thromboembolism used a twice-daily weight-adjusted regimen. However, 2 studies, 1 of patients with acute venous thrombosis\textsuperscript{34} and 1 of patients with acute pulmonary embolism,\textsuperscript{35} used a once-daily dose (175 anti-Xa units/kg) of the same LMWH (Tinzaparin). Both studies

\begin{table*}[h]
\centering
\caption{Efficacy and Safety of 2 Trials Using Outpatient LMWH}
\begin{tabular}{|l|c|c|c|c|}
\hline
\textbf{Study} & \textbf{Treatment} & \textbf{n} & \textbf{Recurrent Thrombosis, n} & \textbf{Major Bleeding, n} & \textbf{Mean Length of Hospital Stay, d} \\
\hline
Levine et al\textsuperscript{36} & UFH & 253 & 17 & 3 & 6.5 \\
& LMWH & 247 & 13 & 5 & 1.1 \\
Koopman et al\textsuperscript{37} & UFH & 198 & 17 & 4 & 11 \\
& LMWH & 202 & 14 & 1 &  \\
\hline
\end{tabular}
\end{table*}

\begin{table*}[h]
\centering
\caption{Relative Efficacy and Safety of LMWH and Heparin in 2 Trials That Included Patients With Pulmonary Embolism}
\begin{tabular}{|l|c|c|c|c|}
\hline
\textbf{Study} & \textbf{Treatment} & \textbf{n} & \textbf{Recurrent Thrombosis, n (%)} & \textbf{Major Bleeding, n (%)} & \textbf{Death, n (%)} \\
\hline
Columbus et al\textsuperscript{38} & UFH & 511 & 25 (4.9) & 8 (1.6) & 39 (7.6) \\
& LMWH & 510 & 27 (5.3) & 10 (2.0) & 36 (7.1) \\
Simmoneau et al\textsuperscript{35} & UFH & 308 & 6 (1.9) & 5 (1.6) & 14 (4.5) \\
& LMWH & 304 & 5 (1.6) & 3 (1.0) & 12 (3.9) \\
\hline
\end{tabular}
\end{table*}
reported that the LMWH (Tinzaparin) was likely to be as effective UFH.

LMWH in Unstable Angina

Currently, the combination of heparin and aspirin is standard antithrombotic treatment for patients with unstable angina and non–Q-wave myocardial infarction. Although the value of aspirin is well established for this indication, the evidence supporting a benefit for heparin is less certain. The increased convenience and recent success of LMWHs for the treatment of venous thromboembolism have led to their evaluation, administered subcutaneously without laboratory monitoring, in patients with unstable angina and non–Q-wave myocardial infarction. To date, 4 randomized trials comparing LMWHs with UFH have been reported.

The first, which was a small open trial comparing LMWH (nadaparine) and aspirin with UFH and aspirin or aspirin alone, reported that the LMWH reduced the risk of acute myocardial infarction. This promising report was followed by three larger studies in patients with unstable angina.

The first large randomized study was a double-blind, placebo-controlled trial of 1506 patients with unstable angina or non–Q-wave myocardial infarction performed by the FRISC study group. The experimental group received LMWH (dalteparin) 120 U/kg twice daily for 6 days followed by 7500 anti-Xa units of dalteparin once daily for 35 to 45 days, whereas the control group received placebo injections; all patients received aspirin. LMWH was shown to reduce the risk of death or myocardial infarction by >60% at 6 days. Thus, of the 741 patients allocated to receive LMWH, 13 (1.8%) died or developed myocardial infarction compared with 36 of 758 (4.7%) of those who received placebo. The composite end point of death, myocardial infarction, and need for revascularization also showed a significant difference in favor of LMWH (5.4% versus 10.3%). At 40 days, the difference in rates of death and myocardial infarction and of the composite end point persisted. However, there was a cluster of events in the patients assigned LMWH after the high initial dose was replaced by the lower maintenance dose, suggesting that a dose of 7500 anti-Xa units of dalteparin once daily produces inadequate protection even after a 6-day course of high-dose LMWH. At 4 to 5 months of follow-up, the significant difference between the 2 groups in the rates of death, myocardial infarction, or revascularization was no longer evident. The rates for death or myocardial infarction in the control and experimental groups were 15.3% and 14.0% respectively (P=0.18); for death, myocardial infarction, or revascularization, 43.6% and 42.7% (P=0.18), respectively.

The results of this study established the short-term value of LMWH (dalteparin) for the treatment of unstable angina but suggested that protection with high-dose treatment is required for >6 days. Although all patients received aspirin, the control group did not receive UFH, which is the standard treatment in most countries.

A second study, the FRIC study, was then performed. In the first phase, 1482 patients with unstable angina or non–Q-wave infarction were assigned to receive the LMWH dalteparin (120 anti-Xa units/kg twice daily) or UFH (5000 U bolus followed by 1000 U/h) by continuous infusion for 6 days in an open randomized design. In the second phase, which was double blind, patients assigned to LMWH were continued at a dose of 7500 IU once daily or placebo. The results showed that the treatment regimens were equivalent in efficacy and safety (Table 7). At 6 days, the composite outcome of death, myocardial infarction, or recurrent angina was 7.6% in the UFH group and 9.3% in the LMWH group. The corresponding rates of the composite end point of death or myocardial infarction were 3.6% and 3.9%, respectively. Between days 6 and 45, the rate of death, myocardial infarction, or recurrence was 12.3% in both groups. There was no difference in the incidence of major bleeding, which was very low in both groups.

The results of this study are consistent with the hypothesis that dalteparin (administered in a dose of 120 anti-Xa IU SC twice daily) is as effective as UFH. It is noteworthy, however, that after 6 days, dalteparin administered in a dose of 7500 U SC once daily is no more effective than placebo, findings that are consistent with the results of the FRISC study.

The third study, the ESSENCE trial, included 3171 patients with unstable angina or non–Q-wave myocardial infarction (Table 7). Patients were randomized in a double-blind fashion to 1 mg/kg (100 anti-Xa IU) SC of LMWH (enoxaparin) every 12 hours or UFH administered as an intravenous bolus followed by a continuous infusion for 2 to 8 days. The median duration of treatment in both groups was 2.6 days. There was a significant reduction in the primary end point of death, myocardial infarction, or recurrent angina at 14 days in patients assigned to LMWH:}

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>n</th>
<th>Death, AMI, or Recurrent Angina, %</th>
<th>Relative Risk Reduction, % (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRIC Study</td>
<td>LMWH</td>
<td>751</td>
<td>21.6</td>
<td>-7.9 (NS)</td>
</tr>
<tr>
<td></td>
<td>UFH</td>
<td>731</td>
<td>19.9</td>
<td></td>
</tr>
<tr>
<td>ESSENCE Study</td>
<td>LMWH</td>
<td>1607</td>
<td>19.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UFH</td>
<td>1564</td>
<td>23.3</td>
<td>15 (0.016)</td>
</tr>
</tbody>
</table>

AMI indicates acute myocardial infarction.
19.8% in the UFH group and 16.5% in the LMWH group, for a 17% relative risk reduction \((P=0.019)\). The 30-day incidence of the composite end point was 23.3% in the UFH group and 19.8% in the LMWH group, which represents a significant difference \((P=0.016)\). This difference was accounted for mainly by a lower incidence of recurrent angina in patients assigned to LMWH, although there was a nonsignificant trend in reduction of death or myocardial infarction.

There was no difference in the incidence of major bleeding at 30 days (6.5% with LMWH versus 7.0% with UFH), but the incidence of total bleeding was higher in the LMWH group (18.4% versus 14.2%), primarily because of bruising at injection sites.

The reason for the differences between the results of the FRIC and ESSENCE studies is uncertain, but there are a number of potential explanations (Table 8).

Dalteparin and enoxaparin are depolymerized by different chemical methods and have different molecular weight distributions. However, these differences are unlikely to explain the more favorable results seen in the ESSENCE study, because patients assigned to receive LMWH in the FRIC study were given a more aggressive anticoagulant regimen (both in terms of anti-Xa and anti-IIa units) than those assigned enoxaparin in the ESSENCE study.

Although the inclusion criteria were similar for both studies, the event rates in the patients assigned UFH appeared to be higher in the ESSENCE study, possibly accounting for the more favorable results in patients assigned LMWH in this study. Alternatively, the observed differences in the efficacy of LMWH in the 2 studies could be due to the play of chance. Further information will be forthcoming from the TIMI 11B trial, which is testing a longer duration of treatment with enoxaparin versus UFH in a similar patient group.

**Controversial Issues**

A number of controversial issues remain, including the relative costs of LMWH and UFH and the possibility that the efficacy and safety of LMWH might be improved if laboratory monitoring is performed.

Although LMWH preparations are more convenient to use than UFH, they have the disadvantage of being more expensive. Because LMWH preparations have not received approval for use for the treatment of venous thrombosis, pulmonary embolism, or unstable angina in the United States, their cost for these indications is unknown. In addition, the higher cost of LMWH preparations cannot be considered in isolation, because they might well be offset by the savings derived from reduced hospital stay and the subcutaneous route of administration.

One appealing feature of LMWH is their more predictable dose response, which has been translated clinically into treatment with weight-adjusted dosing without laboratory monitoring. The only study that compared the predictability of the dose response of LMWH with that of UFH demonstrated less variability with LMWH than with UFH. However, even LMWH produced a somewhat variable anticoagulant response, thereby raising the possibility that both the efficacy and safety of LMWH might be improved if the anti-factor Xa level were monitored. It is likely, however, that if monitoring produces improvement in clinical outcome, the effects would be marginal and therefore would be offset by the loss of convenience and increased expense. Weight-adjusted dosing could be misleading in renal insufficiency or in the very obese, and studies are required to determine if monitoring is necessary in such patients. However, on the basis of current information, when indicated, LMWH preparations should be administered with weight-adjusted dosing in most patients.

**Summary**

LMWHs are a new class of anticoagulants that have pharmacokinetic and biological advantages over UFH. These advantages are translated clinically into (1) greater convenience afforded by the ability to administer LMWH by subcutaneous injection without laboratory monitoring and the associated

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**TABLE 8. Comparison of LMWH Treatment Characteristics and Some Patient Characteristics of the FRIC and ESSENCE Studies**

<table>
<thead>
<tr>
<th>FRIC (n=1482)</th>
<th>ESSENCE (n=3171)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LMWH characteristics</strong></td>
<td><strong>Dalteparin</strong></td>
</tr>
<tr>
<td>Dose</td>
<td>120 anti-Xa (IU)/kg SC twice daily for 6 d</td>
</tr>
<tr>
<td>Anti-Xa:anti-IIa ratio</td>
<td>2.5:1</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>Unstable angina or non–Q-wave infarction</td>
</tr>
<tr>
<td>Heparin regimen</td>
<td>5000 U IV bolus followed by continuous infusion of 1000 U/h with target APTT of 1.5×control</td>
</tr>
<tr>
<td><strong>Results in heparin group</strong></td>
<td></td>
</tr>
<tr>
<td>Death or AMI or recurrent angina</td>
<td>7.6% at 6 d</td>
</tr>
<tr>
<td></td>
<td>19.9% at 45 d</td>
</tr>
<tr>
<td>Death or AMI</td>
<td>3.6% at 6 d</td>
</tr>
<tr>
<td></td>
<td>8.3% at 45 d</td>
</tr>
</tbody>
</table>

SC indicates subcutaneous; AMI, acute myocardial infarction.
cost reduction resulting from reduced hospital stay and (2) a lower incidence of HIT and possibly a lower risk of osteo-
poria. LMWHs appear to be as safe and effective as UFH for the treatment of venous thrombosis and pulmonary embolism and at least as safe and effective as UFH for the treatment of patients with unstable angina. Whether 1 LMWH preparation is more effective than others remains an open question that can be answered only by direct comparison of different LMWH preparations in randomized trials.

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**Key Words:** heparin ■ angina ■ venous thrombosis
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Jack Hirsh

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