Heparin and Low-Molecular-Weight Heparin
Mechanisms of Action, Pharmacokinetics, Dosing, Monitoring, Efficacy, and Safety

Jack Hirsh, MD, FCCP, Chair; Theodore E. Warkentin, MD; Stephen G. Shanghnessy, PhD; Sonia S. Anand, MD; Jonathan L. Halperin, MD; Robert Raschke, MD, MS; Christopher Granger, MD; E. Magnus Ohman, MBBCh, FCCP; and James E. Dolen, MD, MPH, Master FCCP

Abbreviations: ACT = activated clotting time; APTT = activated partial thromboplastin time; AT = antithrombin; AT-III = antithrombin III; CI = confidence interval; DVT = deep vein thrombosis; GP = glycoprotein; HIT = heparin-induced thrombocytopenia; INR = international normalized ratio; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NQMI = non-Q-wave myocardial infarction; OR = odds ratio; PE = pulmonary embolism; PF4 = platelet factor 4; PTA = percutaneous coronary angioplasty; RR = relative risk; sc = subcutaneous; tPA = tissue plasminogen activator; UA = unstable angina; UFH = unfractionated heparin (CHEST 2001; 119:64S–94S)

Heparin and its derivative, low-molecular-weight heparin (LMWH), are the anticoagulants of choice when a rapid anticoagulant effect is required, because their onset of action is immediate when administered by IV injection. Both types of heparins are administered in lower doses for primary prophylaxis than for treatment of venous thrombosis or acute myocardial ischemia. Heparin has pharmacokinetic limitations not shared by LMWHs. Based on these pharmacokinetic limitations, heparin therapy is usually restricted to the hospital setting, where its effect can be monitored and its dosage adjusted frequently. In contrast, LMWH preparations can be administered in either the in-hospital or out-of-hospital setting because they can be administered subcutaneously (sc) without the need for laboratory monitoring. When long-term anticoagulant therapy is indicated, heparin or LMWH administration is usually followed by treatment with oral anticoagulants. However, long-term out-of-hospital treatment with heparin or LMWH is used when anticoagulant therapy is indicated in pregnancy and in patients who develop recurrent venous thromboembolism while treated with appropriate doses of oral anticoagulants.

Since our report in 1998 (Supplement to CHEST, Vol. 114, iss 5), a number of LMWH preparations have been approved for use for the treatment of venous thrombosis and for the treatment of unstable angina (UA).

CLINICAL INDICATIONS

Heparin is effective and indicated for the prevention of venous thromboembolism; for the treatment of venous thrombosis and pulmonary embolism (PE); for the early treatment of patients with UA and acute myocardial infarction (MI); for patients who undergo cardiac surgery using cardiopulmonary bypass; vascular surgery, and coronary angioplasty; in patients with coronary stents; and in selected patients with disseminated intravascular coagulation.

LMWHs are effective and indicated for the prevention of venous thromboembolism, for the treatment of venous thrombosis, for the treatment of acute PE, and for the early treatment of patients with UA. The levels of evidence and grading of recommendations for the clinical use of heparin and LMWHs are discussed in the chapters that consider the evidence supporting antithrombotic therapy with these agents for the various clinical indications.

This chapter will review the mechanisms of action of heparin and LMWHs, their pharmacokinetics, anticoagulant effects, side effects, and laboratory monitoring. The clinical uses of heparin and LMWHs and the results of clinical trials will also be discussed, although more details appear in other chapters.

HISTORICAL HIGHLIGHTS

Heparin was discovered by McLean in 1916, and Brinkhous and associates demonstrated that its anticoagulant effect requires a plasma cofactor later named antithrombin III (AT-III), but is now known simply as antithrombin (AT). Rosenberg and Lami, Rosenberg and Bauer, and Lindahl et al elucidated the mechanisms responsible for the heparin/AT interaction. It is now known that the active center serine of thrombin and other coagulation enzymes is inhibited by an arginine-reactive site on the AT molecule and that heparin binds to lysine on AT, producing a conformational change at the arginine-reactive site that converts AT from a slow, progressive thrombin inhibitor to a very rapid inhibitor of thrombin and factor Xa. AT binds covalently to the active serine centers of coagulation enzymes; heparin then dissociates from the ternary complex and can be reutilized (Fig 1). Subsequently, it was discovered that heparin binds to and potentiates the activity of AT through a unique glucosamine unit contained within a pentasaccharide sequence, the structure of which has been confirmed. A synthetic pentasaccharide has been developed and is undergoing clinical evaluation for prevention and treatment of venous thrombosis.

MECHANISM OF ACTION

Only about one third of an administered dose of heparin binds to AT, and this fraction is responsible for most of its anticoagulant effect. The remaining two thirds has minimal anticoagulant activity at therapeutic concentrations, but at concentrations greater than usually obtained clinically, both high-affinity and low-affinity heparin catalyze the AT effect of a second plasma protein, heparin cofactor II (Table 1).

The heparin-AT complex inactivates a number of coagulation enzymes, including thrombin factor (IIa), factors Xa, IXa, XIa, and XIIa. Of these, thrombin and factor Xa are most responsive to inhibition, and human thrombin is about 10-fold more sensitive to inhibition by the heparin-AT complex than factor Xa (Fig 2). To inhibit throm-
bin, heparin must bind to both the coagulation enzyme and AT, but binding to the enzyme is less important for the inhibition of activated factor X (factor Xa; Fig 3).7 Molecules of heparin containing < 18 saccharides do not bind simultaneously to thrombin and AT and are therefore unable to catalyze thrombin inhibition. In contrast, very small heparin fragments containing the high-affinity pentasaccharide sequence catalyze inhibition of factor Xa by AT.14–17 By inactivating thrombin, heparin not only prevents fibrin formation but also inhibits thrombin-induced activation of factor V and factor VIII.18–20 Unfractionated heparin (UFH) and LMWH also induce secretion of tissue factor pathway inhibitor by vascular endothelial cells that reduce procoagulant activity of tissue factor VIIa complex, and this could contribute to the antithrombotic action of heparin and LMWH.21–23

Heparin is heterogeneous with respect to molecular size, anticoagulant activity, and pharmacokinetic properties (Table 2). Its molecular weight ranges from 3,000 to 30,000 daltons average, with a mean molecular weight of 15,000 daltons (approximately 45 monosaccharide chains; Fig 4).24–26 Its anticoagulant activity varies because only one third of heparins have anticoagulant function and because its anticoagulant profile and clearance are influenced by the

<table>
<thead>
<tr>
<th>Effects</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Binds to AT-III and catalyzes inactivation of factors IIa, Xa, IXa, and XIIa</td>
<td>Major mechanism for anticoagulant effect, produced by only one third of heparin molecules (those containing the unique AT-III-binding pentasaccharide).</td>
</tr>
<tr>
<td>Binds to heparin cofactor II and catalyzes inactivation of factor IIa</td>
<td>Anticoagulant effect requires high concentrations of heparin and occurs to the same degree whether or not the heparin has high or low affinity for AT-III.</td>
</tr>
<tr>
<td>Binds to platelets</td>
<td>Inhibits platelet function and contributes to the hemorrhagic effects of heparin. High-molecular-weight fractions have greater effect than low-molecular-weight fractions.</td>
</tr>
</tbody>
</table>
chain length of the molecules, with the higher-molecular-weight species cleared from the circulation more rapidly than the lower-molecular-weight species. This differential clearance results in accumulation in vivo of the lower-molecular-weight species, which have a lower ratio of antifactor IIa to antifactor Xa activity. The lower-molecular-weight species that are retained in vivo are measured by the antifactor Xa heparin assay, but these have little effect on the activated partial thromboplastin time (APTT). Binding of heparin to von Willebrand factor also inhibits von Willebrand factor-dependent platelet function.27

Heparin binds to platelets, and depending on the experimental conditions in vitro, can either induce or inhibit platelet aggregation.28,29 Heparin prolongs the bleeding time in humans30 and enhances blood loss from the microvasculature in rabbits.31–33 The interaction of heparin with platelets31 and endothelial cells32 may contribute to heparin-induced bleeding by a mechanism independent of its anticoagulant effect.33

In addition to its anticoagulant effect, heparin increases vessel wall permeability,32 inhibits the proliferation of vascular smooth muscle cells,34 and suppresses osteoblast formation and activates osteoclasts that promote bone loss.35,36 Each of these effects is independent of its anticoagulant activity, but only the osteopenic effect is likely to be relevant clinically.37

**Pharmacology of UFH**

The preferred routes of UFH administration are continuous IV infusion and sc injection. When the sc route is selected, the initial dose must be sufficient to overcome the lower bioavailability associated with this route of administration.38 An immediate anticoagulant effect requires an IV bolus.

In the circulation, heparin binds to a number of plasma proteins (Fig 5), which reduces its anticoagulant activity at low concentrations, thereby contributing to the variability of the anticoagulant response to heparin among patients with thromboembolic disorders39 and to the laboratory phenomenon of heparin resistance.40 Heparin also binds
to endothelial cells and macrophages, which further complicates its pharmacokinetics.

Heparin clearance involves a combination of a rapid saturable and a much slower first-order mechanisms (Fig 6). The mechanism of the saturable phase of heparin clearance is through binding to receptors on endothelial cells and macrophages where it is depolymerized (Fig 5), while the slower unsaturable mechanism is renal (Fig 6). At therapeutic doses, heparin is cleared predominantly through the rapid saturable, dose-dependent mechanism and its anticoagulant effects are nonlinear, with both the intensity and duration of effect rising disproportionately with increasing dose. As a result, the half-life of heparin increases from approximately 30 min following an IV bolus of 25 U/kg, to 60 min with a bolus of 100 U/kg, and to 150 min with a bolus of 400 U/kg.

Plasma recovery of heparin is reduced when administered by subcutaneous injection in low (5,000 U q12h) or moderate (12,500 to 15,000 U q12h) doses. At high therapeutic doses (>35,000 U/24 h), however, plasma recovery is almost complete. The difference between the bioavailability of heparin administered by subcutaneous or IV injection was demonstrated in patients with venous thrombosis randomized to receive either 15,000 U q12h by subcutaneous injection or 30,000 U by continuous IV infusion; both regimens were preceded by a 5,000-U bolus. Therapeutic heparin levels and APTT ratios were achieved at 24 h in only 37% of patients given subcutaneous heparin, compared with 71% of those given the same total dose by continuous IV infusion.

**Laboratory Monitoring**

Randomized trials show a relationship among heparin dose, efficacy, and safety. Since the anticoagulant response to heparin varies among patients with thromboembolic disorders, it is standard practice to adjust the dose of heparin and monitor its effect by measurement of the APTT that is sensitive to the inhibitory effects of heparin on thrombin, factor Xa, and factor IXa. Although a relationship exists between heparin dose and therapeutic efficacy for patients with venous thromboembolism, such a relationship has not been established for patients with acute coronary ischemia, although those receiving concomitant thrombolytic therapy or glycoprotein IIb/IIIa antagonists given heparin in a dose used to treat venous thrombosis have an unacceptably high rate of bleeding.

Although a close relationship between the effect of heparin ex vivo on the APTT and its clinical effect in vivo has been assumed, the data supporting this assumption are derived from retrospective subgroup analysis of cohort studies and are inconsistent with the results of a randomized trial and meta-analyses of contemporary cohort studies. Furthermore, there was no

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Table 2—Heterogeneity of UFH

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular size</td>
<td>Mean molecular weight, 15,000 d</td>
</tr>
<tr>
<td></td>
<td>Range, 3,000 to 30,000 d</td>
</tr>
<tr>
<td>Anticoagulant activity</td>
<td>Only one third of heparin molecules contain the high-affinity</td>
</tr>
<tr>
<td></td>
<td>pentasaccharide required for anticoagulant activity</td>
</tr>
<tr>
<td>Clearance</td>
<td>High-molecular-weight moieties are cleared more rapidly than lower-molecular-weight moieties</td>
</tr>
</tbody>
</table>

**Figure 4.** Molecular weight distributions of LMWHs and heparin.
direct relationship between APTT and efficacy observed in the subgroup analysis of the GUSTO I study\textsuperscript{65} in patients with acute MI who were treated with thrombolytic therapy followed by heparin. And even if the APTT were predictive of clinical efficacy, its value would be limited by the variable responsiveness of commercial APTT reagents to heparin.\textsuperscript{66}

The risk of heparin-associated bleeding increases with dose\textsuperscript{67,68} and with concomitant thrombolytic therapy\textsuperscript{69-72} or the GPIIb/IIIa antagonist abciximab.\textsuperscript{54,55} The risk of bleeding is also increased by recent surgery, trauma, invasive procedures, or concomitant hemostatic defects.\textsuperscript{73}

Despite its limitations, the APTT remains the most frequently used method for monitoring the anticoagulant response to heparin. The APTT should be measured approximately 6 h after the bolus dose of heparin, and the continuous IV dose should be adjusted based on the result.

When heparin is given by sc injection in a dose of

\begin{figure}
\centering
\includegraphics[width=\columnwidth]{heparin_diagram.png}
\caption{As heparin (small, filled circles) enters the circulation, it binds to heparin-binding proteins (elongated circles), endothelial cells (EC), macrophages (M), and AT-III (egg-shaped circles). Only heparin with the high-affinity pentasaccharide binds to AT-III, but binding to other proteins and to cells is nonspecific and occurs independently of the AT-III binding site.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\columnwidth]{heparin_dosages.png}
\caption{Low doses of heparin clear rapidly from plasma through saturable (cellular) mechanism of clearance. Therapeutic doses of heparin are cleared by a combination of the rapid, saturable mechanism and the slower, dose-independent mechanism of renal clearance. Very high doses of heparin are cleared predominantly through the slower dose-independent mechanism of clearance.}
\end{figure}
35,000 U/24 h in two divided doses,\textsuperscript{52} the anticoagulant effect is delayed for approximately 1 h and peak plasma levels occur at approximately 3 h.

**Dosing Nomograms**

Audits of physician-directed heparin therapy have demonstrated a great deal of variability in dosing decisions.\textsuperscript{74–77} A number of methods for standardizing the management of IV heparin therapy have been published, including heparin dose-adjustment nomograms\textsuperscript{56,78–83} and computer algorithms.\textsuperscript{84,85} Nomograms and computer-assisted dosage adjustment have also been used to manage heparin in conjunction with thrombolytic therapy for patients with MI.\textsuperscript{65,81,85} The weight-adjusted nomogram has been incorporated into the Agency for Health Care Policy and Research guideline for treatment of UA.\textsuperscript{86,87}

A weight-based nomogram using a starting dose of 18 U/kg/h heparin infusion (1,260 U/h for a 70-kg patient; Fig 7) reduced recurrent thromboembolism in a randomized controlled trial (relative risk [RR] = 0.2; 95% confidence interval [CI], 0.05 to 0.91)\textsuperscript{78,88}; the control group, however, received an inadequate initial heparin infusion (1,000 U/h). Several other nomograms utilize initial heparin infusion doses as low as 12 U/kg/h,\textsuperscript{89,90} but the APTT was determined unconventionally\textsuperscript{91} and therefore might not be valid.

<table>
<thead>
<tr>
<th>Source</th>
<th>Condition</th>
<th>Outcome</th>
<th>RR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hull et al\textsuperscript{38}</td>
<td>DVT</td>
<td>Recurrent venous thromboembolism</td>
<td>15.0</td>
</tr>
<tr>
<td>Basu et al\textsuperscript{61}</td>
<td>DVT</td>
<td>Recurrent venous thromboembolism</td>
<td>10.7</td>
</tr>
<tr>
<td>Turpie et al\textsuperscript{51}</td>
<td>Acute MI</td>
<td>Left ventricular mural thrombosis</td>
<td>22.2</td>
</tr>
<tr>
<td>Kaplan et al\textsuperscript{55}</td>
<td>Acute MI</td>
<td>Recurrent MI/angina pectoris</td>
<td>6.0</td>
</tr>
<tr>
<td>Camilleri et al\textsuperscript{57}</td>
<td>Acute MI</td>
<td>Recurrent MI/angina pectoris</td>
<td>13.3</td>
</tr>
</tbody>
</table>

*RR refers to the relative increase in event rates when the rates in patients with subtherapeutic APTT times are compared with the rates in patients whose values are in the therapeutic range.

Two nomograms have been validated independently,\textsuperscript{62,93} both significantly reduced latency to therapeutic APTT levels. Over a 5-year period, voluntary physician use of the nomogram approached 95% at one institution and this was associated with significantly higher initial heparin dosage, shorter time to therapeutic APTT, and no increase in bleeding.\textsuperscript{94}

Weight-adjusted nomograms have also been evaluated in clinical trials in patients with UA. These have used a lower initial infusion rate of 15 U/kg/h.\textsuperscript{95,96} In the OASIS-2 study,\textsuperscript{95} a bolus dose of 5,000 U was followed by an infusion of 15 U/kg/h. More than 80% of patients reached the therapeutic APTT range (60 s and 100 s) within 24 h. In the TIMI-11B study,\textsuperscript{96} a 70-U/kg bolus was followed by an infusion of 15 U/kg/h and the APTT reached 55 to 58 s in 42% of patients within 12 h. A weight-adjusted nomogram has been incorporated into the guidelines for treatment of UA promulgated by the Agency for Health Care Policy and Research.\textsuperscript{86,87}

When a nomogram is used, it is important to determine the appropriate therapeutic range based on the local laboratory reagent and to adapt the recommended dosage adjustments accordingly. For patients with venous thrombosis or PE, the targeted APTT should be equivalent to a heparin level or 0.3 to 0.7 U/mL by antifactor Xa heparin levels.\textsuperscript{97,98} A lower therapeutic range is recommended for patients with acute myocardial ischemia receiving thrombolytic or GPIIb/IIIa antagonist agents, since a lower dose of heparin proved safer and no less effective in these circumstances than the higher-dose regimen established for patients with venous thrombosis. Recognizing that the traditional heparin dosing regimens cause excessive bleeding in patients with acute MI who receive thrombolytic therapy, a therapeutic range corresponding to antifactor Xa levels of 0.14 to 0.34 seems reasonable.\textsuperscript{89} Failure to adapt nomograms to the therapeutic range could result in dangerous errors in heparin therapy.

**Heparin Resistance**

Some patients require higher-than-average doses of heparin to prolong APTT to the therapeutic range. These patients are designated heparin resistant if their daily

### Figure 7. Weight-based nomogram.

<table>
<thead>
<tr>
<th>Initial dose</th>
<th>80 U/kg bolus, then 18 U/kg/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>APTT, &lt; 35 s (&lt;1.2 x control)</td>
<td>80 U/kg bolus, then 4 U/kg/h</td>
</tr>
<tr>
<td>APTT, 35 to 45 s (1.2 to 1.5 x control)</td>
<td>40 U/kg bolus, then 2 U/kg/h</td>
</tr>
<tr>
<td>APTT, 46 to 70 s (1.5 to 2.3 x control)</td>
<td>No change</td>
</tr>
<tr>
<td>APTT, 71 to 90 s (2.3 to 3 x control)</td>
<td>Decrease infusion rate by 2 U/kg/h</td>
</tr>
<tr>
<td>APTT, &gt; 90 s (&gt;3 x control)</td>
<td>Hold infusion 1 h, then decrease infusion rate by 3 U/kg/h</td>
</tr>
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heparin requirement is >35,000 U/24 h, and approximately 25% of patients with venous thromboembolism fulfill this criterion. Heparin resistance has been associated with AT deficiency and increased heparin clearance. Elevations in hepatic binding proteins and a variety of factors (VIII, fibrinogen, and platelet factor 4 (PF4)) have been reported to cause drug-induced heparin resistance, though the association with nitroglycerin is controversial.111 Factor VIII or fibrinogen levels are elevated in response to acute illness or pregnancy. Elevation of the levels of factor VIII alters the response of the APTT to heparin without diminishing the antithrombotic effect, as the anticoagulant effect of heparin is modified by heparin (measured by the APTT) and the antithrombotic effect measured by anti-Xa activity becomes dissociated. Studies in experimental animals demonstrated that the infusion of factor VIII significantly lowers APTT values without interfering with the antithrombotic effect of heparin. Under these experimental circumstances, heparin concentration was unperturbed and was a more accurate measure of thrombus inhibition than the APTT. A randomized, controlled trial has shown that adjusting dosage by anti-Xa heparin concentrations results in favorable clinical outcomes in heparin-resistant patients despite lower doses of heparin and subtherapeutic APTT levels.

For patients who require >35,000 U of UFH per 24 h, the dose should be adjusted to maintain anti-Xa heparin levels of 0.35 to 0.70 IU/mL. In a randomized, controlled trial in 131 patients with venous thromboembolism requiring >35,000 U of heparin per day, monitoring the APTT was compared to anti-Xa heparin activity with no significant differences in clinical outcomes, but the group monitored using anti-Xa heparin concentrations required significantly less heparin with no difference in bleeding. This approach is especially useful for patients at high risk of bleeding when continued heparin therapy is necessary. Substitution of LMWH may be inadvisable in such patients due to its long half-life and the lack of an effective neutralizing agent. Although measurement of AT levels has also been recommended in the management of heparin resistance, low values are usually secondary to heparin therapy, rather than the cause of heparin resistance.

**Limitations**

The limitations of heparin are based on its pharmacokinetic, biophysical, and its nonanticoagulant biological properties. All of these limitations are caused by the AT-independent, charge-dependent binding properties of heparin to proteins and surfaces. Pharmacokinetic limitations are caused by the following: (1) AT-independent binding of heparin to plasma proteins, and possibly to endothelial cells, which result in the variable anticoagulant response to heparin and to the phenomenon of heparin resistance; and (2) AT-independent binding to macrophages and endothelial cells, which result in its dose-dependent mechanism of clearance.

The biophysical limitations occur because the heparin/AT complex is unable to inactivate factor Xa in the prothrombinase complex and thrombin bound to fibrin or to subendothelial surfaces. The biological limitations of heparin include osteopenia and heparin-induced thrombocytopenia (HIT). Osteopenia is caused as a result of the binding of heparin to osteoblasts, which then release factors that activate osteoclasts, whereas HIT results from heparin binding to PF4 to form an epitope to which the HIT antibody binds. The pharmacokinetic and nonanticoagulant biological limitations of heparin are less evident with LMWH, while the limited ability of the heparin-AT complex to fibrin-bound thrombin and factor Xa is overcome by several new classes of AT-independent thrombin and factor Xa inhibitors.

The anticoagulant effect of heparin is modified by platelets, fibrin, vascular surfaces, and plasma proteins. Platelets limit the anticoagulant effect of heparin by protecting surface factor Xa from inhibition by heparin/AT and by secreting PF4, a heparin-neutralizing protein. Fibrin limits the anticoagulant effect of heparin by protecting fibrin-bound thrombin from inhibition by heparin/AT. Heparin binds to fibrin and bridges between fibrin and the heparin binding site on thrombin. As a result, heparin increases the affinity of thrombin for fibrin, and by occupying the heparin binding site on thrombin, protects fibrin-bound thrombin from inactivation by heparin/AT. Thrombin also binds to subendothelial matrix proteins, where it is protected from inhibition by heparin. These observations explain why in experimental animals and patients, heparin is less effective than the AT-independent thrombin and factor Xa inhibitors at preventing thrombosis at sites of deep arterial injury and may explain why hirudin is more effective than heparin in UA and non-Q-wave myocardial infarction (NQMI).

**Therapeutic Use**

Heparin is indicated for prevention of venous thromboembolism; for treatment of venous thrombosis and PE for the early treatment of patients with UA and acute MI; for patients who undergo cardiac surgery using cardiopulmonary bypass, vascular surgery, coronary angioplasty, and stents; and in selected patients with disseminated intravascular coagulation. LMWHs are indicated for prevention of venous thromboembolism, for treatment of venous thrombosis, for treatment of acute PE, and for the early treatment of patients with UA. Levels of evidence and grading of recommendations for the clinical use of heparin and LMWHs are discussed in the chapters discussing antithrombotic therapy for the various clinical indications.

In patients with venous thromboembolism or UA, the dose of heparin is usually adjusted to maintain the APTT at an intensity equivalent to an antifactor Xa level of 0.35 to 0.7 U/mL. For many APTT reagents, this is equivalent to a ratio (patient/control APTT) of 1.5 to 2.5. This therapeutic range is recommended based on animal studies and subgroup analysis of prospective studies of patients with established deep vein thrombosis (DVT) and studies of prevention of mural thrombosis after MI and prevention of recurrent ischemia following coronary
thrombolysis. Recommended heparin regimens for venous and arterial thrombosis are summarized in Table 4.

TREATMENT OF VENOUS THROMBOEMBOLISM

The efficacy and safety of continuous IV infusion of heparin has been compared with intermittent IV injection in seven studies and with high-dose sc injection in five studies. From these studies, it is difficult to determine the optimal route of heparin administration because most were underpowered, total doses varied, and disparate criteria were used to assess outcome. A pooled analysis of 11 clinical trials involving 15,000 patients found the mean bolus of 5,000 U followed by 30,000 to 35,000 U/24 h with APTT monitoring or sc LMWH found the mean incidence of recurrent venous thromboembolism 5.4% (fatal in 0.7%) and major bleeding 1.9% (fatal in 0.2%).

A 5-day course of heparin therapy appears as effective as a 10-day course for the treatment of DVT (Table 5). and brevity has obvious appeal, reducing both hospital stay and the risk of HIT. While adequate for most patients with venous thromboembolism, a 5-day course of heparin therapy may not be sufficient for those with extensive iliofemoral venous thrombosis or PE who were underrepresented in these studies.

PROPHYLAXIS AGAINST VENOUS THROMBOEMBOLISM

Heparin in a fixed low dose of 5,000 U sc every 8 to 12 h results in 60 to 70% risk reduction for venous thrombosis and fatal PE. The incidence of fatal PE in general surgical patients was reduced from 0.7% in control subjects to 0.2% in one analysis (p < 0.001), and from 0.8 to 0.3% (p < 0.001) in a larger analysis that included orthopedic surgical patients. There was also a statistically significant decrease in mortality, from 3.3 to 2.4% (p < 0.02). The use of low-dose heparin was associated with a small excess of wound hematoma, but there was no statistically significant increase in major bleeding. Low-dose heparin therapy is also effective for prevention of venous thromboembolism in patients with MI and other serious medical disorders, reducing in-hospital mortality by 31% (p < 0.05) in a study of 1,358 general medical patients > 40 years old. The incidence of DVT remains substantial (20 to 30%) after hip surgery, despite low-fixed-dose heparin prophylaxis, and risk can be reduced further by administering either adjusted-dose heparin or fixed-dose LMWH. Moderate-dose warfarin therapy is also effective in patients undergoing major orthopedic surgical procedures, but direct comparisons of low-dose heparin and warfarin therapy have not been performed in patients undergoing major orthopedic surgery in sufficiently powered trials.

CORONARY ARTERY DISEASE

Coronary thrombosis is important in the pathogenesis of UA, acute MI, and sudden cardiac death, and affects the outcomes of patients with acute MI treated with thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA). Heparin is no longer used as the sole antithrombotic drug in patients with acute coronary syndromes, but it is combined with aspirin in eligible patients with acute MI, with thrombolytic therapy in patients with evolving MI, and with GPIIb/IIIa antagonists in high-risk patients with UA or in those undergoing high-risk PTCA. Heparin increases the risk of bleeding when given in full doses combined with aspirin, thrombolytic therapy, and GPIIb/IIIa antagonists, so the dose is usually reduced in these settings.

UNSTABLE ANGINA AND NQMI

Heparin has been evaluated in a number of randomized, double-blind, placebo-controlled clinical trials for the short-term treatment of patients with UA or NQMI. When used alone in patients with UA, heparin reduces the risk of developing recurrent angina or acute MI. Meta-analysis of short-term results suggests that the combination of heparin and aspirin reduces cardiovascular death and MI by about 30% over that achieved by aspirin alone.

Theroux et al compared the relative efficacy and safety of heparin, aspirin, or the combination in 479 patients with UA. The incidence of MI during the acute period was 11.9% in the placebo group and was reduced to 3.3% in the aspirin group (p = 0.012), 0.8% in the heparin group (p < 0.0001), and 1.6% with the combination (p = 0.001; all comparisons to placebo). The incidence of refractory angina, 22.9% in the placebo group, was reduced

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Recommended Heparin Regimen*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thromboembolism</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis of DVT and PE</td>
<td>5,000 U sc q8h or q12h or adjusted low-dose heparin</td>
</tr>
<tr>
<td>Treatment of DVT</td>
<td>5,000 U IV bolus followed by 32,000 U q24h by IV infusion or 35,000 to 40,000 U q24h sc, adjusted to maintain APTT in the therapeutic range</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td></td>
</tr>
<tr>
<td>UA or acute MI without thrombolytic therapy</td>
<td>5,000 U IV bolus followed by 32,000 U q24h IV infusion adjusted to maintain APTT in the therapeutic range</td>
</tr>
<tr>
<td>Acute MI after thrombolytic therapy†</td>
<td>5,000 U IV bolus followed by 24,000 U q24h adjusted to maintain APTT in the therapeutic range</td>
</tr>
</tbody>
</table>

*APTT varies in responsiveness to heparin.
†Role of heparin unproven.
duced to 8.5% with heparin (p = 0.002), 10.7% with heparin plus aspirin (p = 0.11), but it was 16.5% in the aspirin group. In a second study, these investigators compared heparin with aspirin, eliminating the placebo and combination therapy groups. Fatal or nonfatal MI occurred in 4 of 362 heparin-treated patients, compared with 23 of 362 patients treated with aspirin (odds ratio = 0.16; p < 0.005).

In contrast, the Research Group in Instability in Coronary Artery Disease159 found heparin (10,000 U q6h for 24 h and 7,500 U q6h for 5 days thereafter) no more effective than aspirin (75 mg/d) in 796 men with UA or NQMI. The incidence of MI or death 5 days after enrollment was significantly reduced only in the group given the combination of aspirin plus heparin (1.4%, p = 0.027), and not in the groups receiving either heparin or aspirin alone. After 30 days and 90 days, both the aspirin and aspirin-plus-heparin groups fared significantly better than those given placebo, but the outcome in the group receiving heparin alone was no different than placebo.

A meta-analysis of published data from six randomized trials, each relatively small (composite n = 1,353) including the foregoing, found a risk reduction of 33% in cardiovascular death and MI (95% CI, 2 to 56%) with the combination of IV UFH and aspirin compared to placebo, but this was of borderline statistical significance (Fig 8).155 When data from the FRISC trial,228 which compared LMWH to placebo in patients treated with aspirin, are also considered, the combination of heparin and aspirin appears more effective than aspirin alone in patients with UA.

**Acute MI**

The benefit of heparin in patients with acute MI not given thrombolytic therapy may not be applicable to the current clinical practice of treating these patients with aspirin. In randomized trials before the thrombolytic era, heparin reduced reinfarction by an average of 22% and mortality by 17%.164 Heparin also reduces the incidence of mural thrombosis.56 A fixed dose of 12,500 U sc q12h reduced the incidence of mural thrombosis detected by two-dimensional echocardiography by 72% compared with no treatment,165 and by 58% compared with low-dose heparin (5,000 U sc q12h; p < 0.06 for each study).166

**Coronary Thrombolysis**

Although in the past it was generally accepted that heparin is effective after coronary thrombolysis, the results of recent studies have cast doubt on this view. In both the International Study Group167 and the ISIS-3168 studies, adjunctive heparin, 12,500 U sc q12h, in patients receiving thrombolytic therapy plus aspirin produced only marginal benefit at the price of increased bleeding. The delayed sc heparin regimen used in

---

**Table 5—Comparison of Long and Short Courses of Heparin Therapy in the Treatment of Proximal Vein Thrombosis**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Gallus et al146 (n = 266)</th>
<th>Hull et al103 (n = 199)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short Course, 4 d</td>
<td>Long Course, 9.5 d</td>
</tr>
<tr>
<td>Recurrent VTE, %</td>
<td>3.6</td>
<td>4.7</td>
</tr>
<tr>
<td>During heparin treatment</td>
<td>3.3</td>
<td>1.6</td>
</tr>
<tr>
<td>During warfarin treatment</td>
<td>6.9</td>
<td>6.3</td>
</tr>
</tbody>
</table>

*VTE = venous thromboembolism.*

---

**Figure 8.** RR of MI or death during hospitalization.
the ISIS-3 trial proved no better or worse than high-dose IV heparin (5,000 U initially followed by infusion of 1,000 to 1,200 U/hr to maintain APTT 60 to 55 s) among patients with acute MI receiving streptokinase in the GUSTO trial in terms of patency of the infarct-related artery, reinfarction hemorrhage, or mortality.165

In a much smaller study of 250 patients randomized to treatment with either aspirin alone or aspirin plus weight-adjusted IV heparin infusion beginning 4 h after anisoylated plasminogen streptokinase activator complex infusion, there were no differences in ischemic outcomes, but overall bleeding was significantly greater with heparin (32% vs 17.2%; p = 0.006).166

A meta-analysis of trials of thrombolytic therapy in patients with acute MI, largely driven by the International Study Group and the ISIS-3 studies, found that when aspirin is also used, heparin reduced mortality by only 6% (95% CI, 0 to 10%; p = 0.03), translating to five fewer deaths per 1,000 treated patients; three fewer reinfarctions (p = 0.04), and one fewer PE (p = 0.01; Table 6). This relatively small benefit was counterbalanced by three major bleeds per 1,000 patients treated with heparin (p < 0.0001) and an insignificant trend toward excess stroke.170

Data on the role of adjunctive heparin in patients treated with tissue plasminogen activator (tPA) are limited. From contemporary studies, Kruse and associates171 concluded that the role of heparin as adjunctive treatment to accelerated tPA is still an open issue. Among six randomized trials involving tPA therapy, there was a trend toward reduction of in-hospital mortality (odds ratio [OR] = 0.91; 95% CI, 0.59 to 1.39), but a significantly higher rate of hemorrhagic complications with heparin.172

Accordingly, the American College of Cardiology/American Heart Association guidelines for management of patients with acute MI suggest adjusting the intensity of heparin based on the type of thrombolytic agent used and the presence or absence of risk factors for systemic embolism.173

**CORONARY ANGIOPLASTY**

PTCA can be complicated by early thrombotic occlusion. It is standard practice to administer either as an IV bolus of 10,000 U with repeated smaller injections as required, or as a weight-adjusted dose of 100 to 175 U/kg followed by infusion of 10 to 15 U/kg/hr to maintain the activated clotting time (ACT) at >300 to 350 s. There is evidence that the complication rate is higher with lower ACT values.174 When these high-dose regimens are used in combination with abciximab and aspirin, however, heparin increases the risk of major bleeding.12,175 The risk can be reduced without compromising efficacy by lowering the initial bolus dose of heparin to 70 U/kg, adjusting subsequent doses to raise ACT of >200 s, and removing arterial sheaths when ACT falls to <150 to 180 s.155 Postprocedural heparin infusions are not needed for most patients after coronary angioplasty, who are treated with a combination of aspirin and ticlopidine or aspirin and clopidogrel.

**LMWHs**

**Historical Perspective**

The development of LMWHs for clinical use was stimulated by three main observations. Compared to UFH, LMWH displayed the following: (1) reduced anti-factor IIa activity relative to antifactor Xa activity,12,175; (2) a more favorable benefit-risk ratio in experimental animals; and (3) superior pharmacokinetic properties.182–187 Of these potential advantages, only the pharmacokinetics are of clear clinical importance.122,188

In 1976, Johnson et al175 and Andersson et al12 reported that LMWH fractions prepared from standard commercial-grade heparin had progressively less effect on the APTT, as they were reduced in molecular size, while still inhibiting activated factor X (factor Xa). The APTT activity of heparin reflects mainly its antifactor IIa activity. The disassociation of antifactor Xa activity from its effect on antithrombin (IIa) activity (expressed as an APTT measurement) challenged the prevailing biophysical model for the anticoagulant effect of heparin, which predicted that any heparin molecule, irrespective of chain length, would catalyze the inactivation of serine protease coagulation enzymes equally, provided it contained the high-affinity binding site for AT. The difference in anticoagulant profile between LMWH and UFH was elucidated in the United States and in Sweden (Table 7).15,16,189–193

Evidence that LMWH produces less microvascular bleeding than UFH in experimental models176–181 has not been borne out in human studies involving prevention and treatment of venous thrombosis, PE, or UA. In these studies, LMWH and UFH were associated with similar rates of bleeding.

| Table 6—Effect of Heparin With or Without Aspirin in Coronary Thrombolysis: Overview of 26 Randomized Trials* |
|--------------------------------------------------|-----------|--------|-------------|-----------|
| Variables | No Aspirin (n = 5,459) | p Value | Aspirin (n = 68,090) | p Value |
| Death | 35 | 0.002 | 5 | 0.03 |
| Reinfarction | 15 | 0.08 | 3 | 0.04 |
| Stroke | 10 | 0.01 | 1 | 0.01 |
| Major bleeding | 10 more | 0.01 | 3 more | < 0.001 |

*Data are presented as reduction per 1,000 patients assigned heparin. Adapted from Collins et al.158
Anticoagulant Effects

failure. LMWH preparations have a longer plasma half-life and better bioavailability at low doses than UFH, which is explained by the relatively lower binding properties of the smaller fragments in circulation and cellular proteins (Table 9). Compared to UFH, LMWHs have less ability to inactivate thrombin because the smaller fragments cannot bind simultaneously to both AT and thrombin. However, since bridging between AT and factor Xa is less critical for antifactor Xa activity, the smaller fragments inactivate factor Xa almost as well as do larger molecules.

The anticoagulant, pharmacokinetic, and other biological differences between UFH and LMWH can be explained by the relatively lower binding properties of LMWH to circulating and cellular proteins. Compared to UFH, LMWHs have less ability to inactivate thrombin because the smaller fragments cannot bind simultaneously to both AT and thrombin. However, since bridging between AT and factor Xa is less critical for antifactor Xa activity, the smaller fragments inactivate factor Xa almost as well as do larger molecules.

LMWHs are derived from heparin by chemical or enzymatic depolymerization, yielding fragments approximately one third the size of heparin. The various LMWHs approved for use in Europe, Canada, and the United States are shown in Table 8. Since they are prepared by different methods of depolymerization, they differ to some extent in pharmacokinetic properties and anticoagulant profile, and may not be clinically interchangeable. LMWHs have a mean molecular weight of 4,500 to 5,000 d, with a distribution of 1,000 to 10,000 d.

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**Structure and Pharmacology**

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**Anticoagulant Effects**

Like UFH, LMWHs produce their major anticoagulant effect by activating AT. The interaction with AT is mediated by a unique pentasaccharide sequence found on fewer than one third of LMWH molecules. Since a minimum chain length of 15 saccharides (including the pentasaccharide sequence) is required to form ternary complexes among heparin, AT, and thrombin, only the minority of LMWH species that are above this critical chain length are available to inactivate thrombin. In contrast, all LMWH chains containing the high-affinity pentasaccharide catalyze the inactivation of factor Xa (Fig 3). Since virtually all heparin molecules contain at least 15 saccharide units, UFH has an antifactor Xa to antifactor IIa ratio near unity. In contrast, the ratios of commercial LMWHs range between 2 and 4 depending on molecular weight distribution.

**Monitoring LMWH in Patients With Obesity or Renal Failure**

Laboratory monitoring of LMWH therapy is usually not necessary. In certain clinical situations, such as morbid obesity and renal failure, however, the dose can be difficult to determine. Although dosing studies have not been carried out in these special populations, monitoring has been suggested. Several laboratory assays have been proposed, including the Heptest (Sigma-Aldrich Canada; Oakville, Ont) and the chromogenic anti-Xa assay; the latter is more widely available and currently recommended by the College of American Pathologists. The minimal therapeutic levels have not been established definitively, but anti-Xa levels were found to be inversely related to thrombus propagation in some studies. High anti-Xa levels (> 0.8 U/mL at steady state) in patients receiving therapeutic doses of LMWH have also been associated with bleeding in some experimental animal and clinical studies. The best time to perform an anti-Xa assay (if indicated in renal failure or morbid obesity) is 4 h after sc injection of a weight-adjusted dose of LMWH. For twice-daily administration, a conservative therapeutic range is 0.6 to 1.0 IU/mL. The target range at 4 h is less clear in patients treated with LMWH once daily, but 1.0 to 2.0 IU/mL is reasonable. Although weight-adjusted dosing has not been evaluated in patients with severe obesity, it would be prudent to check an anti-Xa level after the first few doses in these patients, but once the correct dose is established, repeated testing is unnecessary.

Randomized trials of LMWH either excluded patients with renal failure or failed to specify

<table>
<thead>
<tr>
<th>Agent</th>
<th>Manufacturer/Location</th>
<th>Method of Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danaparoid sodium (Orgaran)</td>
<td>NV Osogon/Oss, Netherlands</td>
<td>Nitrous acid depolymerization</td>
</tr>
<tr>
<td>Reviparin (Clivarine)</td>
<td>Knoll/Markham, Ont</td>
<td>Prepared from animal gut mucosa; contains heparin sulfate (84%), dermatan sulfate (12%), and chondroitin sulfate (4%)</td>
</tr>
<tr>
<td>Dalteparin (Fragmin)</td>
<td>Pharmacia/Peakack, NJ</td>
<td>Nitrous acid depolymerization</td>
</tr>
<tr>
<td>Enoxaparin sodium (Lovenox/Clexane)</td>
<td>Aventis/Collegeville, PA</td>
<td>Benzylation followed by alkaline depolymerization</td>
</tr>
<tr>
<td>Nadroparin calcium (Fraxiparin)</td>
<td>Sanofi/Gentilly, France</td>
<td>Nitrous acid depolymerization</td>
</tr>
<tr>
<td>Ardeparin (Normiflo)</td>
<td>Wyeth-Ayerst/Philadelphia, PA</td>
<td>Peroxidative depolymerization</td>
</tr>
<tr>
<td>Tinzaparin (Innohep)</td>
<td>Leo Laboratories/Dublin, Ireland</td>
<td>Enzymatic depolymerization with heparinase</td>
</tr>
<tr>
<td>Randomized trials of LMWH either excluded patients with renal failure or failed to specify</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 7—Relationship Between Molecular Weight and Anticoagulant Activity of Heparin Fractions**

<table>
<thead>
<tr>
<th>Heparin Oligosaccharides</th>
<th>Molecular Weight</th>
<th>Anti-Xa</th>
<th>Anti-IIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>2,400</td>
<td>1.3</td>
<td>Nil</td>
</tr>
<tr>
<td>12</td>
<td>3,600</td>
<td>2.58</td>
<td>Nil</td>
</tr>
<tr>
<td>16</td>
<td>4,800</td>
<td>1.60</td>
<td>Nil</td>
</tr>
<tr>
<td>18</td>
<td>5,400</td>
<td>0.95</td>
<td>0.51</td>
</tr>
<tr>
<td>24</td>
<td>7,200</td>
<td>1.30</td>
<td>1.21</td>
</tr>
</tbody>
</table>

*Data from Lane et al.*

**Table 8—Commercial LMWHs and a Heparinoid: Methods of Preparation**

<table>
<thead>
<tr>
<th>Agents</th>
<th>Method of Preparation</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>24</td>
<td>7,200</td>
<td>1.30</td>
<td>1.21</td>
</tr>
</tbody>
</table>
Possible Antineoplastic Effects of LMWH

In 1992, two clinical trials comparing LMWH to UFH in the treatment of venous thromboembolism demonstrated unexpected reductions in death from cancer.102,220 A meta-analysis145 of 629 cancer patients from nine clinical trials demonstrated that the odds ratio for 3-month cancer mortality was 0.65 (95% CI, 0.40 to 0.93) for LMWH compared to UFH. The hypothesis that LMWH might have anticaner effects was not considered a priori in the design of these trials, so the results observed in the meta-analysis must be considered exploratory. However, the observed results are consistent with animal studies, which have shown that LMWH inhibits metastasis212,213 and angiogenesis necessary for tumor growth234,235. Currently, several trials are underway to evaluate the effects of LMWH preparations on mortality in patients with cancer and thrombosis.

Clinical Applications

Prevention of Venous Thrombosis

LMWHs were first evaluated for the prevention of venous thrombosis in high-risk surgical patients in the mid-1980s, and considerable experience has been gained for this indication. In general surgical patients and in high-risk medical patients, low doses of LMWHs admin-

Table 9—Biological Consequences of Reduced Binding of LMWH to Proteins and Cells

<table>
<thead>
<tr>
<th>Binding Targets</th>
<th>Biological Effects</th>
<th>Clinical Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin</td>
<td>Reduced anti-IIa to anti-Xa ratio</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 HIT</td>
</tr>
<tr>
<td>Osteoblasts</td>
<td>Reduced activation of osteoclasts</td>
<td>Lower incidence of osteopenia</td>
</tr>
</tbody>
</table>

whether such patients were recruited.219,222,225,226 When LMWH is administered to patients with renal failure, it is prudent to check anti-Xa levels periodically to avoid accumulation to toxic levels.

Anti-Xa assays in use throughout North America are highly variable: one specimen tested in 46 laboratories yielded mean LMWH anti-Xa activity of 0.7 IU/mL with a SD of 0.1, and a range of 0.8 to 1.0 IU/mL.206

Oral Heparin

Heparin is not normally absorbed from the GI tract.229 Chemical delivery agents (N-acylated amino acids) have been synthesized that can form noncovalent bonds with heparin and facilitate absorption across intestinal epithelium.230,231 Animal studies have demonstrated antithrombotic effects,232 and 30,000 U of an oral preparation increased APTT values in healthy volunteers from 28 to 42 s (p < 0.01) and anti-Xa levels to 0.2 ± 0.05 IU/mL.233 Several clinical trials are now underway to investigate clinical applications of oral heparin preparations.

LMWHs proved safe and effective for prevention of thromboembolism in two well-designed randomized trials of patients undergoing noncardiovascular surgery. One trial236 in 4,498 patients found a statistically significant reduction in thromboembolic mortality with LMWH (0.07%) compared with UFH (0.36%). In contrast, a meta-analysis237 of randomized trials comparing low-dose UFH with LMWH reported minimal differences between the two forms of prophylaxis.

Orthopedic Surgery

Compared to placebo, LMWHs produced a 70 to 79% risk reduction for venous thrombosis in two studies,238,239 without an increase in major bleeding. There was a small increase in minor bleeding with LMWH in a third study,240 but none was sufficiently powered to exclude a modest increase in major bleeding.

LMWHs have been compared with a variety of other methods of prophylaxis, including low-dose UFH,241–243 adjusted-dose heparin,244,245 dextran,246,247 and warfarin.248 In most studies performed in North America, LMWH therapy was started postoperatively, the first dose administered 12 to 24 h after surgery, which increased the acceptability of prophylaxis among surgeons. This approach is particularly appealing in view of concerns about the risk of spinal cord hematoma when anticoagulant prophylaxis is used in conjunction with spinal anesthesia. In such cases, the first dose of LMWH should be delayed until after the epidural catheter has been removed; when this is not possible, the catheter should be removed at least 8 h after the last dose of LMWH. Under these circumstances, other drugs that impair hemostasis (such as nonsteroidal anti-inflammatory agents) should be avoided.

A meta-analysis240 of randomized studies comparing prophylactic LMWH with fixed low-dose or adjusted-dose UFH reported an incidence of venous thrombosis of 13.9% in the group given LMWH and 21.7% in the heparin groups (p = 0.01), with a lower incidence of
proximal venous thrombosis in the LMWH group (5.4% vs 12.5%; p < 0.0001). There was no difference in the rates of bleeding between the two groups (Table 10). These results are comparable to those of an earlier meta-analysis.237

In two studies, LMWH was compared to low-dose UFH for prevention of venous thrombosis after elective knee arthroplasty. The incidences of venous thrombosis were 23% and 24.6% in the LMWH groups compared with 27% and 34.2% in the heparin groups, respectively.250,251 The difference was statistically significant in one study250 but not the other study251 and there was no difference in the incidence of bleeding between the two types of heparin in either study.

Comparison of LMWH With Oral Anticoagulants

LMWH preparations have been compared with warfarin and other oral anticoagulants in six studies involving high-risk orthopedic surgical patients.252–259 The efficacy of the LMWH preparations was equal to warfarin in patients undergoing elective hip replacement, but superior in patients undergoing major knee surgery (Table 11). In several of these studies, LMWH was associated with a slightly greater incidence of major bleeding.

Hip Fracture

There have been two randomized trials with the LMWH danaparoid sodium in patients with fractured hips. In one, the incidence of thrombosis was 13% in patients given danaparoid sodium compared with 35% in patients given dextran (p < 0.001).240 Transfusion requirements were significantly higher in the dextran group. In the other trial, venous thrombosis occurred in 44.8% of patients treated with aspirin vs 27.8% treated with danaparoid sodium (p < 0.05); there was no difference in bleeding rates.

Multiple Trauma

LMWH (enoxaparin sodium; 30 mg sc q12h) was compared with UFH (5,000 U q12h); treatment with each was started within 36 h of multiple trauma. The incidence of venous thrombosis was 31% among 129 patients in the LMWH group vs 44% among 136 patients allocated to UFH (p = 0.014). The incidence of proximal venous thrombosis was 6% in the LMWH group vs 15% in the low-dose UFH group (p = 0.09).261 Major bleeding occurred in 0.6% with UFH and 2.9% with LMWH.

Summary of LMWH in Orthopedic Surgery and Trauma

Overall, LMWHs appear effective for prevention of venous thromboembolism and safe in high-risk patients undergoing major orthopedic surgical procedures. Compared to placebo, the RR reduction for all thrombi and for proximal vein thrombosis is approximately 70%. LMWHs are more effective than low-dose UFH, at least as effective as warfarin, and more effective than dextran or aspirin in patients undergoing total hip arthroplasty, and more effective than warfarin, aspirin, or dextran in patients undergoing major knee surgery. Similarly, LMWHs are more effective than aspirin in patients with hip fracture. The risk of bleeding with LMWH is comparable to low-dose UFH or warfarin.

Neurosurgery

In a study comparing LMWH plus compression stockings with compression stockings alone, those assigned to LMWH had a risk reduction of 48%. There was no difference in major bleeding.

Medical Patients

LMWH has been compared to placebo in two studies of patients with ischemic stroke263,264 and has been compared with low-dose heparin in two studies.265,266 Compared with placebo, LMWHs reduce the risk of venous thrombosis between 40% and 86% without an increase in clinically important bleeding, and in studies comparing LMWH with UFH, the reduction in risk of thrombosis was > 70% with LMWH.144,266

Treatment of Venous Thromboembolism

A number of well-designed studies have compared LMWH preparations with UFH in patients with venous thrombosis or PE. A meta-analysis of randomized studies published up to 1996, in which four different LMWH preparations administered by sc injection in unmonitored weight-adjusted doses were compared with IV UFH, found similar rates of recurrent thromboembolism and major bleeding with each type LMWH and with APTT-guided IV UFH (Tables 12, 13). Following publication of this analysis, five additional trials253,217,218,225,226 have been completed, two involving patients with venous thrombosis,218,225 one in patients with venous thrombosis or PE,226 one in patients with PE,217 and one in patients with proximal vein thrombosis were also randomized to inferior

Table 10—Meta-analysis of Randomized Studies Comparing LMWH and Heparin in Elective Hip Surgery

<table>
<thead>
<tr>
<th>Factors</th>
<th>Proximal Venous Thrombosis</th>
<th>Total Venous Thrombosis</th>
<th>Major Bleeding</th>
<th>Minor Bleeding</th>
<th>PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common OR*</td>
<td>0.40</td>
<td>0.70</td>
<td>0.64</td>
<td>0.90</td>
<td>0.30</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.28–0.59</td>
<td>0.53–0.92</td>
<td>0.34–1.23</td>
<td>0.61–1.33</td>
<td>0.09–1.02</td>
</tr>
</tbody>
</table>

*OR < 1 favors LMWH over heparin. Data from Anderson et al.

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vena cava filter insertion. In two of the studies, patients assigned to LMWH were encouraged to administer treatment at home, while those assigned to UFH were treated conventionally with a continuous IV infusion in hospital. Patients with symptomatic PE or previous venous thrombosis were excluded. Out-of-hospital administration of LMWH to eligible patients with DVT was as effective and safe as IV heparin administered in hospital (Table 14). In the COLUMBUS study, 1,021 patients with venous thrombosis or PE were randomized to treatment with either sc LMWH (reviparin sodium) or IV adjusted-dose UFH for 8 days. Warfarin therapy was started concomitantly and continued for 3 months. The mean hospital stay was 3 days shorter in patients assigned to LMWH, while rates of recurrent thromboembolism, bleeding, and mortality were similar in both groups. The relative efficacy and safety of LMWH and UFH have also been investigated in a larger population: 612 patients with acute PE who did not require thrombolytic therapy or pulmonary embolectomy were randomized to regimens of LMWH (tinzaparin, 175 anti-Xa U/kg sc qd) or heparin (50 U/kg IV bolus followed by an infusion of 500 U/kg/d) adjusted to an aPTT ratio of 2.0 to 3.0, for prevention of recurrent thromboembolism, major bleeding, and death. By day eight, 9 of 308 patients (2.9%) assigned to UFH and 9 of 304 patients (3.0%) assigned to LMWH developed primary events; by day 90, 22 patients (7.1%) assigned to UFH and 18 patients (5.9%) assigned to LMWH developed events (p = 0.54; Table 15). The rate of major bleeding was similar in both groups (2.6% and 2.0%, respectively; not significant). There were 3 deaths at 8 days and 14 deaths (4.5%) at 90 days in those assigned to UFH, and 4 deaths at 8 days and 12 deaths (3.9%) at 90 days in patients assigned to LMWH. Five deaths in the heparin group were treatment related (three from PE and two from major bleeding), compared to four deaths in the LMWH group (three from PE and one from bleeding). Taken together with the results of the COLUMBUS study, the data indicate that sc LMWH is as effective and safe as IV UFH.

A meta-analysis of 11 randomized studies comparing IV UFH and sc LMWH in about 3,500 patients with acute DVT (Table 16) found less major bleeding with LMWH (OR = 0.57; p = 0.05). The frequency of recurrent thromboembolic events did not differ significantly between treatment groups (OR = 0.85; p = 0.28), but mortality was lower in those assigned LMWH (OR = 0.71; p = 0.02). Most deaths were not ascribed to PE, so the mechanism for this reduction is uncertain.

Most studies evaluating LMWH preparations for the treatment of venous thromboembolism evaluated a twice-daily, weight-adjusted regimen. However, two studies using tinzaparin, one in patients with acute venous thrombosis and the other in patients with acute PE, found

### Table 11—Controlled Trials With LMWH in Elective Total Knee Surgery

<table>
<thead>
<tr>
<th>Source</th>
<th>LMWH</th>
<th>DVT</th>
<th>Venous Thrombosis Proximal</th>
<th>Major Hemorrhage</th>
<th>Control</th>
<th>DVT</th>
<th>Venous Thrombosis Proximal</th>
<th>Major Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hull et al</td>
<td>Tinzaparin</td>
<td>116/258</td>
<td>20/258</td>
<td>9/317</td>
<td>Warfarin</td>
<td>152/277</td>
<td>34/227</td>
<td>3/324</td>
</tr>
<tr>
<td>RD Heparin Group</td>
<td>Ardeparin</td>
<td>41/149</td>
<td>7/149</td>
<td>NA</td>
<td>Warfarin</td>
<td>60/147</td>
<td>15/147</td>
<td>NA</td>
</tr>
<tr>
<td>Leclerc et al</td>
<td>Enoxaparin sodium</td>
<td>8/41</td>
<td>0/41</td>
<td>0/66</td>
<td>Placebo</td>
<td>35/54</td>
<td>11/54</td>
<td>1/65</td>
</tr>
<tr>
<td>Fauno et al</td>
<td>Enoxaparin sodium</td>
<td>29/92</td>
<td>3/92</td>
<td>NA</td>
<td>Heparin</td>
<td>25/93</td>
<td>5/93</td>
<td>NA</td>
</tr>
<tr>
<td>Colwell et al</td>
<td>Enoxaparin sodium</td>
<td>54/145</td>
<td>4/145</td>
<td>3/28</td>
<td>Heparin</td>
<td>74/143</td>
<td>22/143</td>
<td>3/225</td>
</tr>
</tbody>
</table>

*Data are presented as No./total patients (%). NA = not available. Data from Colwell et al.

### Table 12—LMWH vs Heparin in the Treatment of DVT: Symptomatic Recurrent Venous Thromboembolic Complications During Initial Treatment and During 3-mo to 6-mo Follow-up

<table>
<thead>
<tr>
<th>Agents</th>
<th>LMWH</th>
<th>Heparin</th>
<th>RR Reduction (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadroparin</td>
<td>20/361 (5.5)</td>
<td>32/355 (9.0)</td>
<td>40 (~5-66)</td>
<td>0.07</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>6/213 (2.8)</td>
<td>15/219 (6.9)</td>
<td>59 (~1-83)</td>
<td>0.07</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>13/314 (4.1)</td>
<td>20/320 (6.3)</td>
<td>35 (~3-68)</td>
<td>0.23</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>16/322 (5.0)</td>
<td>8/339 (2.4)</td>
<td>~110 (~374-7)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Data are presented as No./total patients (%) unless otherwise indicated. Data from Kuijer et al.
once-daily administration of 175 anti-Xa U/kg as effective and safe as twice-daily dosing.221,227

Unstable Angina and NQMI

Although the combination of heparin and aspirin is effective for short-term treatment of patients with UA, within 1 month between 6% and 15% progress to MI or death, despite continuing aspirin therapy.69,268 LMWHs have been evaluated in seven randomized trials of patients with UA or NQMI (Table 17). The combined rate of MI, recurrent angina, and urgent coronary revascularization was significantly lower in a small (n = 219) open trial with the LMWH nadroparin plus aspirin than with UFH plus aspirin alone.222 A larger, double-blind, placebo-controlled trial in 1,506 aspirin-treated patients with UA or NQMI228 compared dalteparin 120 anti-Xa u/kg bid for 6 days followed by 7,500 U qd, with placebo treatment. LMWH reduced the risk of death or MI by approximately 80% at 6 days compared to placebo treatment. The composite rate of death, MI, and revascularization was significantly lower in patients treated with LMWH (10.3% vs 5.4%) over 35 to 45 days, but after 4 to 5 months, the difference between these event rates in the placebo and dalteparin groups was

*Data are presented as No./total patients (%) unless otherwise indicated. Data from Kuijer et al.267

Table 13—LMWH vs Heparin: Incidence of Major Bleeding Complications During Initial Heparin Treatment, Including 48 h After Heparin Treatment Cessation*

<table>
<thead>
<tr>
<th>Agent</th>
<th>LMWH</th>
<th>Heparin</th>
<th>RR Reduction (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadroparin</td>
<td>4/446 (0.9)</td>
<td>10/436 (2.3)</td>
<td>59 (−16–86)</td>
<td>0.09</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>1/213 (0.5)</td>
<td>11/219 (5.0)</td>
<td>91 (−0.9)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>5/314 (1.6)</td>
<td>3/320 (0.9)</td>
<td>70 (−580–58)</td>
<td>&gt; 0.2</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>2/433 (0.5)</td>
<td>5/464 (1.0)</td>
<td>55 (−99–90)</td>
<td>&gt; 0.2</td>
</tr>
</tbody>
</table>

Table 14—Efficacy and Safety of Two Trials Using Outpatient LMWH for the Treatment of Venous Thromboembolism

<table>
<thead>
<tr>
<th>Source</th>
<th>Treatment</th>
<th>Patients, No.</th>
<th>Recurrent Thrombosis, No.</th>
<th>Major Bleeding, No.</th>
<th>Mean Length of Hospital Stay, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levine et al218</td>
<td>UFH</td>
<td>253</td>
<td>17</td>
<td>3</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>LMWH</td>
<td>247</td>
<td>13</td>
<td>5</td>
<td>1.1</td>
</tr>
<tr>
<td>Koopman et al225</td>
<td>UFH</td>
<td>198</td>
<td>17</td>
<td>4</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>LMWH</td>
<td>202</td>
<td>14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 15—Relative Efficacy and Safety of LMWH and Heparin in Two Trials That Included Patients With PE*

<table>
<thead>
<tr>
<th>Source</th>
<th>Treatment</th>
<th>Patients, No.</th>
<th>Recurrent Thrombosis</th>
<th>Major Bleeding</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Columbus226</td>
<td>UFH</td>
<td>511</td>
<td>25 (4.9)</td>
<td>8 (1.6)</td>
<td>39 (7.6)</td>
</tr>
<tr>
<td></td>
<td>LMWH</td>
<td>510</td>
<td>27 (5.3)</td>
<td>10 (2.0)</td>
<td>36 (7.1)</td>
</tr>
<tr>
<td>Simonneau et al217</td>
<td>UFH</td>
<td>308</td>
<td>6 (1.9)</td>
<td>5 (1.6)</td>
<td>14 (4.5)</td>
</tr>
<tr>
<td></td>
<td>LMWH</td>
<td>304</td>
<td>5 (1.6)</td>
<td>3 (1.0)</td>
<td>12 (3.9)</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%) unless otherwise indicated.

Unstable Angina and NQMI

Although the combination of heparin and aspirin is effective for short-term treatment of patients with UA, within 1 month between 6% and 15% progress to MI or death, despite continuing aspirin therapy.69,268 LMWHs have been evaluated in seven randomized trials of patients with UA or NQMI (Table 17). The combined rate of MI, recurrent angina, and urgent coronary revascularization was significantly lower in a small (n = 219) open trial with the LMWH nadroparin plus aspirin than with UFH plus aspirin alone.222 A larger, double-blind, placebo-controlled trial in 1,506 aspirin-treated patients with UA or NQMI228 compared dalteparin 120 anti-Xa u/kg bid for 6 days followed by 7,500 U qd, with placebo treatment. LMWH reduced the risk of death or MI by approximately 80% at 6 days compared to placebo treatment. The composite rate of death, MI, and revascularization was significantly lower in patients treated with LMWH (10.3% vs 5.4%) over 35 to 45 days, but after 4 to 5 months, the difference between these event rates in the placebo and dalteparin groups was

Table 16—LMWH vs Heparin for Treatment of DVT: Summary of Meta-analysis Results*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Subjects, No.</th>
<th>Summary OR†</th>
<th>NNT, No.</th>
<th>Frequency in UFH Group, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>3,674</td>
<td>0.57‡</td>
<td>164</td>
<td>1.9</td>
</tr>
<tr>
<td>RTE</td>
<td>3,566</td>
<td>0.85</td>
<td>114</td>
<td>5.4</td>
</tr>
<tr>
<td>Mortality (overall)</td>
<td>3,566</td>
<td>0.71†</td>
<td>61</td>
<td>6.8</td>
</tr>
</tbody>
</table>

*RTE = recurrent thromboembolism; NNT = number needed to treat. Adapted from Gould et al.145
†A summary OR < 1.0 favors LMWH; a summary OR > 1.0 favors UFH.
‡p < 0.05.
no longer statistically significant. This study established the short-term effectiveness of LMWH (dalteparin) in combination with aspirin for treatment of UA and NQMI, and supported a beneficial effect of heparin plus aspirin over aspirin alone in this population.

In a third study,223 which used an open randomized design in 1,492 patients with UA or NQMI, dalteparin (120 anti-Xa U/kg bid) was compared with UFH (5,000 U IV bolus followed by 1,000 U/h infusion for 6 days), followed by a second, double-blind phase comparing LMWH at a dose of 7,500 U qd with placebo treatment. All patients received aspirin. Both regimens were equivalent in terms of efficacy and safety. The ESSENCE trial,224 one of two that compared enoxaparin with UFH, randomized 3,171 patients with UA or NQMI to enoxaparin, 1 mg/kg sc (100 anti-Xa U) q12h, or UFH as an IV bolus followed by a continuous infusion, for 2 to 8 days (median, 2.6 days; Table 17). There was a 17% reduction in death, MI, or recurrent angina at 14 days with LMWH (median, 2.6 days; Table 17). There was a 17% reduction in death, MI, or recurrent angina at 14 days with LMWH (p = 0.019), and a 15% reduction at 30 days (p = 0.016). This difference was due mainly to a lower incidence of recurrent angina in patients assigned to LMWH. There was no difference in major bleeding (6.5% with LMWH vs 7.0% with UFH at 30 days), but minor bleeding was more frequent with LMWH (18.4% vs 14.2%), mainly bruising at injection sites. The difference in primary event rates remained significant after a year (p = 0.022).269

The TIMI-11B study was the other double-blind study comparing enoxaparin with IV UFH in 3,910 patients with UA or NQMI. The primary outcome was death, MI, or urgent revascularization at 43 days.266 Patients randomized to LMWH therapy who did not experience bleeding or surgery continued treatment at a lower dose, and those randomized to UFH therapy received placebo until day 43, when a 12% risk reduction was observed (p = 0.048). An absolute risk reduction of 2.3% was apparent at 14 days, and no additional benefit of LMWH developed with longer treatment.

In the FRAXIS trial,270 patients with UA or NQMI were randomly assigned to treatment with abbreviated sc nadroparin (q12h for 6 days, then placebo from day 7 to day 14), sustained sc nadroparin (q12h for 14 days), or initial IV UFH for 6 days followed by placebo until day 14. The rate of vascular death, MI, or recurrent angina was no different among the three groups at 6 days, or between short-term and long-term treatment with LMWH by 14 days. In the FRISC-II trial,271 2,267 patients with UA or NQMI received dalteparin, 120 U/kg q12 h for 5 to 7 days, and then either dalteparin, 5,000 to 7500 U q12h, or placebo for 90 days. The primary outcome, death or MI at 3 months, did not differ between groups, but bleeding was more frequent in patients who received dalteparin. Compared with UFH, an overview of trials reveals a 15 to 20% relative reduction in risk of MI or death during 7 to 14 days of treatment with LMWH.91,224 Based on available data from approximately 10,000 patients with UA, however, treatment with LMWH does not offer long-term benefit over placebo in reducing MI or death (OR = 1.04; 95% CI, 0.79 to 1.37; Fig 9).

Q-Wave MI

In patients with Q-wave acute MI, experience with LMWH is limited to two small studies, in which most patients received thrombolytic therapy. The Fragmin in Acute Myocardial Infarction study272 enrolled 776 patients with acute anterior MI in a randomized, double-blind comparison of LMWH (dalteparin, 150 U/kg sc bid) with placebo. Thrombolytic therapy (streptokinase) and aspirin were administered to > 90% of patients. The mean time to the start of treatment was approximately 12 h. After an average of 9 days, left ventricular mural thrombus or system embolism developed in 35 of 247 patients (14.2%) receiving dalteparin vs 59 of 270 patients (21.9%) in the placebo group (p = 0.03). Benefit was limited to inhibition of left ventricular thrombus formation (RR = 0.63; 95% CI, 0.43 to 0.92; p = 0.02) with LMWH, as there were too few events to detect differences between treatments with respect to arterial embolism, reinfarction, or death. LMWH therapy was associated with increases in major (2.9% vs 0.3%; p = 0.006) and minor hemorrhage (14.8% vs 1.8%; p < 0.001). Thus, LMWH reduced mural thrombus formation in patients with acute anterior MI at the price of increased bleeding that may have been related to

### Table 17—Trials of LMWH in Acute Coronary Syndrome Without ST-Segment Elevation*

<table>
<thead>
<tr>
<th>Trials</th>
<th>Patients, No.</th>
<th>Short-term Comparison</th>
<th>Long-term Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gurfinkel et al222</td>
<td>219</td>
<td>Nadroparin 214 IU sc bid vs placebo</td>
<td>N/A</td>
</tr>
<tr>
<td>FRISC228</td>
<td>1,506</td>
<td>Dalteparin 120 IU/kg sc bid vs placebo</td>
<td>Dalteparin 7,500 IU sc qd vs placebo</td>
</tr>
<tr>
<td>Klein et al223</td>
<td>1,482</td>
<td>Dalteparin 120 IU/kg sc bid vs UFH 5,000 IU bolus, 1,000 IU/h IV then 12,500 IU sc bid</td>
<td>Dalteparin 7,500 IU sc qd vs placebo</td>
</tr>
<tr>
<td>Cohen et al224</td>
<td>3,171</td>
<td>Enoxaparin 1 mg/kg sc bid 2 to 8 d vs UFH 5,000 IU APTT 55 to 85 s</td>
<td>N/A</td>
</tr>
<tr>
<td>Antman et al26</td>
<td>3,912</td>
<td>Enoxaparin 3,000 IU bolus, 100 IU/kg bid vs UFH 70 IU bolus, 15 U/kg APTT 1.5 to 2.0</td>
<td>Enoxaparin 4,500 to 6,000 IU sc bid vs placebo</td>
</tr>
<tr>
<td>Leizorivitz270</td>
<td>3,468</td>
<td>Nadroparin 87 IU sc bid vs UFH 5,000 IU bolus 1,250/h target local APTT</td>
<td>Nadroparin 87 IU sc vs placebo</td>
</tr>
<tr>
<td>FRISC II271</td>
<td>2,457</td>
<td>Dalteparin 120 IU/kg bid vs placebo</td>
<td>Dalteparin 5,000 IU or 7,500 IU sc bid vs placebo</td>
</tr>
</tbody>
</table>

*N/A = not applicable.
concomitant thrombolytic therapy and use of a higher dose of dalteparin than given in either the Fragmin in Acute Myocardial Infarction Study \(^{272}\) or the Fragmin in Unstable Coronary Artery Disease Trial \(^{223}\). In a study \(^{273}\) of 103 streptokinase-treated patients randomly assigned to enoxaparin or placebo therapy within 5 days of acute MI, 2 of 43 patients in the enoxaparin group (4.3%) developed recurrent MI within 30 days, compared to 12 of 60 patients receiving placebo treatment (20%; \(p = 0.02\)).

**Coronary Angioplasty**

Animal studies indicating that LMWH suppresses neo-intimal proliferation following arterial balloon injury \(^{274,275}\) prompted clinical trials to evaluate the effect of LMWH on restenosis after angioplasty. In the Enoxaparin Restenosis after Angioplasty trial \(^{276}\), there was no difference in rates of restenosis among patients randomized to treatment with enoxaparin, 40 mg sc qd, or placebo for 1 month following successful coronary angioplasty. Although minor bleeding was more frequent in the enoxaparin group, rates of major bleeding did not differ significantly. The Enoxaparin and MaxEPA for the Prevention of Angioplasty Restenosis study \(^{277}\) randomized 653 patients to treatment with either enoxaparin (30 mg sc bid) or placebo for 6 weeks following successful angioplasty after factorial randomization to either fish oil or control a median of 6 days earlier. Quantitative coronary angiography revealed no significant difference in rates of restenosis either per patient or per lesion. These two studies leave little doubt about the lack of efficacy of enoxaparin for prevention of restenosis when applied in doses up to 60 mg/d (6,000 anti-Xa U/d) for 6 weeks.

**Overcoming the Anticoagulant Effect of Heparin**

The anticoagulant effect of UFH can be neutralized rapidly by IV protamine, a cationic protein derived from fish sperm that binds strongly to (anionic) heparin in a ratio of approximately 100:1000 U/mL of protamine; 50 mg of protamine would therefore be required immediately following a 5,000-U IV heparin bolus to counteract the anticoagulant effect. When infused, only the heparin given during the preceding several hours should be included in the dose calculation, since the half-life of IV UFH is approximately 60 min. A patient receiving an infusion of 1,250 U/h needs approximately 30 mg of protamine. Neutralization of heparin after a sc dose may require a prolonged infusion or a repeated injection of protamine. A fall in APTT can be used to confirm heparin neutralization. \(^{278}\)

The risks of severe adverse reactions to protamine, such as hypotension and bradycardia, are reduced by slow administration over 1 to 3 min. \(^{279}\) Allergic reactions, including anaphylaxis, are associated with previous exposure to protamine-containing insulin, eg, neutral protamine Hagedorn insulin, vasectomy, and hypersensitivity to fish. \(^{278,280,281}\) Patients at risk of developing antiprotamine antibodies can be pretreated with corticosteroid and antihistamine medications. \(^{278}\)

Other methods to overcome the effects of heparin include hexadimethrine, \(^{282,283}\) heparinase (neutralase), \(^{284}\) PF4, \(^{285,286}\) extracorporeal heparin removal devices, \(^{287,288}\) and synthetic protamine variants, \(^{289}\) but these are not widely available.

Protamine neutralizes the antithrombin activity of LMWH, normalizing the APTT and thrombin time, but the cationic protein neutralizes the antifactor Xa activity incompletely, \(^{290–297}\) because protamine exhibits reduced binding to low-molecular-weight components. \(^{122,296,298}\) The clinical significance of incomplete anti-Xa neutralization by protamine is unclear. In animals, protamine overcomes microvascular bleeding in animal models despite incomplete restoration of factor Xa-activity. \(^{298–300}\) But to our knowledge, no published clinical studies demonstrate a beneficial effect of protamine on bleeding complications of LMWH. In animal studies, \(^{301–304}\) synthetic protamine variants have been highly effective in neutralizing LMWH (including anti-Xa activity) and are less toxic than protamine. Of the other reversing agents under investigation,
including synthetic heparin-binding peptide, heparinase-I, and lactoferrin, none are yet available for clinical use.

Recommendations for treatment of LMWH overdose listed below are consistent with package labeling but are clinically untested. Within 8 h of administering LMWH, the dose of protamine is 1 mg/100 anti-Xa u for enoxaparin (1 mg = approximately 100 anti-Xa u). If bleeding continues, a second dose of 0.5 mg protamine/100 anti-Xa U LMWH may be administered. Smaller doses are needed beyond 8 h after LMWH administration.

Nonhemorrhagic Side Effects

HIT

HIT is an antibody-mediated, adverse reaction to heparin, which can cause venous and arterial thrombosis. HIT should be considered a clinicopathologic syndrome, the diagnosis of which is based on both clinical and serologic features.

HIT antibody formation accompanied by otherwise unexplained fall in platelet count > 50% (even if the nadir remains > 150 × 10⁹/L) or skin lesions at injection sites are manifestations of the HIT syndrome.

The antigen is a multimolecular complex of heparin and PF4 (a platelet granule protein of the CXC family of chemokines). HIT antibodies bind to one or more PF4 regions conformationally modified by interaction with heparin or other anions, eg, hypersulfated chondroitin sulfate, pentosan polysulfate, or polyvinylsulfonate. Although at least 18 saccharide units are necessary to bind heparin simultaneously to thrombin and AT, a smaller number (12 to 14 saccharides) is the minimum needed to form the antigenic complex with PF4. Thus, LMWH molecules > 4,000 d can cause HIT, but the risk of antibody formation and clinical HIT is lower during treatment with LMWH than with UFH. Theoretically, very small LMWH preparations (eg, pentasaccharides) or specially engineered heparin preparations (eg, highly sulfated heparin moieties bridged by nonsulfated spacer regions) will not cause HIT.

Figure 9 illustrates the central role of thrombin in the pathogenesis of HIT. In vivo platelet activation results from binding of heparin-PF4-IgG immune complexes to platelet FcIIa receptors. Evidence for thrombin generation in vivo includes markedly elevated levels of thrombin-AT complexes (median, 43 to 44 μg/L), much higher than occur in control patients with postoperative DVT (median, 7.6 μg/L). Factors contributing to thrombin generation could include formation of procoagulant, platelet-derived microparticles; tissue factor expression by endothelium injured by HIT antibodies; and neutralization of heparin by PF4 released from activated platelets. Marked thrombin generation explains several clinical features of HIT, including the hypercoagulable state associated with venous and arterial thrombosis, compensated (hypofibrinogenemic) disseminated intravascular coagulation in 5 to 10% of HIT patients, and progression of DVT to gangrene in some patients with HIT who are treated with warfarin. This iatrogenic syndrome results from disturbing the balance between procoagulant and anticoagulant states during heparin therapy; warfarin causes severe acquired reduction of protein C, while it fails to control thrombin generation. Typically, patients with warfarin-induced venous limb gangrene have international normalized ratio (INR) values > 3.5, due to severely reduced factor VII levels that parallel the fall in protein C. The role for in vivo thrombin generation in HIT provides a rationale for current therapies that emphasize reduction of thrombin generation, either via inhibition of factor Xa (eg, administration of danaparoid) or through direct inhibition of thrombin (eg, lepirudin, argatroban).

The frequencies of HIT antibody formation and clinical HIT vary in different clinical settings. For example, patients undergoing cardiac surgery are more likely than orthopedic surgical patients to form HIT antibodies during treatment with UFH, but orthopedic patients who form HIT antibodies are more likely to develop clinical HIT. Furthermore, HIT occurs less often in medical than surgical patients treated with UFH.

There are two main laboratory assays to detect HIT antibodies. Activation assays exploit the potent platelet-activating properties of HIT serum or plasma in the presence of heparin. Although assays are widely performed with platelet-rich plasma from normal donors, those utilizing washed platelets (eg, platelet serotonin release assay, or the heparin-induced platelet activation assay) are more sensitive and specific, and have been validated in blinded assessment. Antigen assays based on detecting antibodies that recognize PF4 bound to heparin are now commercially available. Antigen assays detect clinically insignificant antibodies more often than activation assays do, however, so physicians must interpret antigen assays cautiously in clinical context.

Treatment of HIT-Associated Thrombosis

Both prospective and retrospective studies indicate that 50 to 75% of patients with HIT develop thrombosis requiring effective anticoagulant therapy, but to our knowledge, only one randomized trial of HIT treatment has been performed to date. Danaparoid sodium is a mixture of anticoagulant glycosaminoglycans with predominant antifactor Xa activity. The rate of thrombus resolution was higher with danaparoid and warfarin than with dextran and warfarin for patients with either mild thrombosis (92% vs 72%; p < 0.04) or severe thrombosis (92% vs 33%; p < 0.001). This small study was unblinded, and only preliminary (1996) data are available. Although generally weak, cross-reactivity can be detected in vitro in a minority of HIT sera, < 5% of patients treated with danaparoid develop evidence suggesting in vitro cross-reactivity; moreover, in vitro cross-reactivity cannot be predicted from in vitro observations. This, plus the generally favorable clinical experience with danaparoid for treatment of HIT, means treatment should not be delayed for cross-reactivity testing. The anticoagulant effect of danaparoid is monitored by chromogenic antifactor Xa assay. Most patients achieve therapeutic levels with standard dosing (Table 18), yet monitoring
is recommended for very small or large patients, those with renal failure, and those with HIT threatening life or limb. Danaparoid does not interfere with INR measurements, which facilitates monitoring of overlapping coagulation factors. Danaparoid has been approved for DVT prophylaxis in the United States, Canada, and most of Europe, although its use for treatment of HIT is predominantly off-label.

Danaparoid is a hirudin derivative manufactured using recombinant technology. Two prospective cohort studies of lepirudin for the treatment of HIT-associated thrombosis using a prespecified dosing schedule and historical control subjects (Table 18) led to its approval for this indication in both the European Union (March 1997) and the United States (March 1998). In one study, the composite end point of mortality, amputation, and thromboembolism was significantly reduced compared with historical control subjects (10% vs 23% at day 7, and 25% vs 52% at day 35, respectively; p = 0.014). In the other study, there was a trend favoring lepirudin. A subgroup analysis of the two studies (pooled) found that a subtherapeutic APTT ratio (<1.5) was associated with an increased risk for thrombosis, whereas an APTT ratio above the therapeutic range (>2.5) was associated with bleeding. Even within the therapeutic range, however, bleeding was significantly greater in treated patients than control subjects (RR = 3.21; 95% CI, 1.7 to 6.0; p < 0.001).

The anticoagulant effect of lepirudin is monitored by the APTT. Lepirudin is renally excreted, and the risks of accumulation and bleeding are high in patients with renal failure. Lepirudin is about 1.3 h. A high proportion of patients develop antihirudin antibodies, which occasionally result in an increase in anticoagulant effects. Thus, ongoing monitoring is recommended throughout the course of lepirudin treatment, even when the initial anticoagulant effect appears stable.

Argatroban is a direct thrombin inhibitor that has been reported to be associated with a lower thrombotic event rate in a prospective cohort study than in historical control subjects. Like lepirudin, the half-life of argatroban is short (<1 h). Argatroban is excreted normally in patients with moderate renal failure, but the dose must be reduced in patients with hepatic failure. Argatroban recently was approved by the US Food and Drug Administration for the treatment and prevention of thrombosis in patients with HIT. A dosing schedule is shown in Table 18.

Warfarin: It has been suggested that warfarin therapy can lead to venous limb gangrene in patients with HIT. However, the frequency of venous limb gangrene among HIT patients treated with coumarin anticoagulants is uncertain. Venous limb gangrene was found in 8 of 66 patients (12%) with HIT-associated DVT who were treated with warfarin in a retrospective study in Hamilton. In some patients, high initial doses of warfarin or concomitant use of anecrd (a defibrinogenating snake venom that is associated with increased thrombin generation) may have contributed to this complication; however, even “usual” doses of warfarin that result in a rise in the INR to supratherapeutic levels can be associated with limb necrosis. Since none of the patients appeared to have an underlying congenital mutation involving the protein C anticoagulant system, it is possible

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**Table 18—Treatment Protocols for Danaparoid, Lepirudin, and Argatroban**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Recommendations</th>
<th>Indications</th>
<th>Dose</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danaparoid</td>
<td>Grade 1B</td>
<td>Rapid therapeutic anticoagulation (IV infusion)</td>
<td>Loading: 2,250-U bolus (1,500 U if &lt; 50 kg; 3,000 U if 75 to 90 kg; 3,750 U if ≥ 90 kg), followed by 400 U/h for 4 h, then 300 U/h for 4 h</td>
<td>150 to 200 U/h to maintain anti-Xa levels between 0.5 U/mL and 0.8 U/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prophylactic anticoagulation (sc injection)</td>
<td>750 U q12h if 75 to 90 kg; 1,500 U q12h if ≥ 90 kg</td>
<td></td>
</tr>
<tr>
<td>Lepirudin (recombinant hirudin)</td>
<td>Grade 1C</td>
<td>Rapid therapeutic anticoagulation (IV infusion)</td>
<td>Loading: 0.4 mg/kg bolus IV</td>
<td>0.15 mg/kg/h IV, with adjustments to maintain APTT 1.5 to 2.5 times the median of the normal laboratory range.</td>
</tr>
<tr>
<td>Argatroban</td>
<td>Grade 2C</td>
<td>Rapid therapeutic anticoagulation (IV infusion)</td>
<td>Initial: 2 μg/kg/min</td>
<td>Above initial dose adjusted to maintain APTT 1.5 to 3.0 times the initial baseline value (not to exceed 100 s)</td>
</tr>
</tbody>
</table>

*All bolus doses are based on 750-U ampule availability.
†If preferred, following initial bolus, danaparoid can still be administered subcutaneously (generally, 1,500 U q8h to q12h).
‡If antifactor Xa levels are not available, danaparoid can still be administered safely for most patients, as there is a high probability of achieving the target anticoagulant range with this regimen, and bleeding complications are uncommon. However, monitoring is recommended for very small and large patients, patients with renal failure, and patients with life- or limb-threatening thrombosis.
§Generally, the anti-Xa level will be 0.1 U/mL on day 1, and rise to 0.15 to 0.35 U/mL by the fifth day (measured midinterval, 6 h after the morning dose).
that increased thrombin generation from HIT contributed to the development of warfarin-induced venous gangrene in these patients. Supporting this supposition were higher ratios of thrombin-AT complexes to protein C activity among patients developing venous gangrene.325

Although there have been other case reports350–352 of warfarin-induced venous limb gangrene, a recent retrospective cohort study353 did not identify any among 51 HIT patients treated with warfarin. Only 16 patients had active DVT when warfarin therapy was commenced, however, and the initial doses of warfarin were lower than in the Hamilton study. Given the risk of thrombosis over the first few days after stopping heparin therapy for HIT, the delayed onset of anticoagulation with coumarin, and the potential for gangrene, we recommend that warfarin not be given as monotherapy for acute HIT or in combination with anced. However, warfarin has not been reported to cause gangrene when combined with an anticoagulant that reduces thrombin generation in HIT (eg, danaparoid or lepirudin).

**LMWH:** Although LMWH is less likely to cause HIT antibody formation,317,318 it is as reactive as UFH in activation assays using washed platelets and HIT sera.318,354 Furthermore, a risk of thrombosis during treatment of HIT with LMWH has been observed.355

Platelet transfusions should be considered as relatively contraindicated in prophylaxis of bleeding in patients with acute HIT336 because petechiae and other signs of bleeding are not clinical features of HIT, despite thrombocytopenia,325 and in anecdotal reports, platelet transfusions have been associated with thrombotic events.357,358 However, if bleeding caused by local lesions or other factors complicates HIT, therapeutic platelet transfusions may be appropriate.

**Treatment of Isolated HIT**

Discontinuation of heparin therapy has long been the cornerstone of management of HIT, but this step alone is not enough even for patients with isolated thrombocytopenia.325,339,345,346,359,360 The risk of thrombosis is still 10% at 2 days, 40% at 7 days, and 50% at 30 days despite stopping heparin therapy in one study339 and 38% in another.353 The incidence of thrombosis was no lower when heparin therapy was stopped <48 h after onset of HIT than when the diagnosis was made later (45% vs 34%; p = 0.26). A high initial rate of thrombosis (10.4% over a mean of 1.7 days before starting lepirudin therapy) was also observed in prospective cohort studies326.

In 16 patients with isolated HIT examined by compression ultrasonography or contrast venography, DVT was identified in 8 patients (all but 1 proximal). These patients were treated with danaparoid in therapeutic dosage, while those without thrombosis received danaparoid in lower prophylactic dosage. One death occurred due to thrombosis.361 The high frequency of DVT when the diagnosis of isolated HIT was established suggests that subclinical thrombosis early during the course of HIT may account for the prevalence of subsequent clinical thromboembolism among patients managed solely by withdrawal of heparin therapy.

Given the unfavorable natural history of isolated HIT and the efficacy and safety of alternative anticoagulation in patients with HIT-associated thrombosis, we recommend administration of another rapidly acting anticoagulant in patients with isolated HIT until the platelet count is restored. Prophylactic doses may be appropriate when subclinical DVT has been excluded by objective studies, but this approach has not been prospectively evaluated.

**Heparin-Induced Osteoporosis**

Heparin or LMWH is usually administered for short periods when an immediate anticoagulant effect is required and coumarins are used for long-term treatment. In pregnancy, however, long-term administration of heparin or LMWH is preferred to prevent and treat venous thromboembolism, to prevent systemic embolism in women with mechanical heart valves, and to prevent fetal loss in women with antiphospholipid antibodies. In patients who are not pregnant, long-term heparin or LMWH therapy is also indicated for recurrent venous thromboembolism after “adequate” oral anticoagulant therapy, and in some immobilized patients requiring prophylaxis for prolonged periods. Clinical trials are ongoing to determine whether long-term therapy with LMWH is useful in outpatients with symptomatic coronary artery disease. In all these instances, the long-term use of heparin or LMWH carries a risk of osteoporosis.362–373

Significant reductions in bone density have been reported in about 30% of patients, and symptomatic vertebral fractures occur in 2 to 3% of patients receiving heparin for 1 month or more. There was a 2.2% incidence of vertebral fracture among 184 women receiving long-term heparin therapy during pregnancy,370 and spinal fractures occurred in 6 of 40 patients receiving 10,000-U UFH sc bid for 3 to 6 months. In the first study,370 only women with severe back pain were tested for fracture; patients in the second study372 were significantly older and were routinely screened for spinal fracture.

Progress in delineating the mechanisms of the effect of heparin on bone has been slowed by the lack of suitable animal models. Studies in Sprague Dawley rats have provided new information on the mechanism of heparin-induced osteoporosis. Animals treated with UFH at doses of 0.25 to 1.0 anti-Xa U/g for 28 days demonstrated a dose-dependent decrease in cancellous bone volume in the distal third of the femur.374 Treatment was associated with a 45% decrease in the number of osteoblasts and a 81% decrease in the amount of unmineralized collagen (osteon) lining the cancellous bone surface. Furthermore, heparin increased osteoclast surface by 58%, indicating that heparin causes bone loss both by decreasing the rate of bone formation and by increasing bone resorption.

The same rat model of heparin-induced osteoporosis was used to explore reversibility when heparin treatment was stopped.375 Rats were randomized to once-daily sc UFH or saline solution for 28 days and followed an additional 28 days off treatment. Based on histomorphometric analysis of the distal third of the right femur proximal to the epiphyseal growth plate, heparin caused a 30% loss in cancellous bone volume over the first 28 days.
accompanied by an increase in osteoclast surface and a decrease in both osteoblast and osteoid surface. Twenty-eight days after stopping heparin therapy, however, there was no improvement in any of these parameters, and serum alkaline phosphatase, a biochemical marker of bone formation, continued to decline. $^{125}$-labeled heparin accumulated in bone and was retained at least 28 days after treatment, which suggests that, following discontinuation of therapy, heparin-induced osteoporosis is not rapidly reversible because heparin is sequestered in bone for extended periods, $^{375}$ possibly bound to bone matrix proteins.

LMWHs may carry a lower risk of osteoporosis than UFH. Dalteparin, 5,000 anti-Xa U sc, was compared with UFH, 10,000 U sc bid, for 3 to 6 months in 80 patients with DVT. $^{373}$ Six of the 40 patients who received UFH developed spinal fractures, compared to 1 patient receiving dalteparin. There was a dose-dependent decrease in cancellous bone volume in rats treated with UFH or the LMWH tinzaparin (0.5 to 1.0 μg) for 32 days, but UFH caused significantly greater cancellous bone loss than LMWH. $^{376}$ Furthermore, although UFH and LMWH decreased osteoblast and osteoid surface similarly, only UFH increased osteoclast surface. Both UFH and LMWH reduced serum alkaline phosphatase, consistent with reduced bone formation, while there is a transient increase in urinary type 1 collagen cross-linked pyridinoline, consistent with an increase in bone resorption. Whereas UFH decreases cancellous bone volume both by decreasing the rate of bone formation and increasing the rate of bone resorption, LMWH causes less osteopenia, decreasing only the rate of bone formation. $^{376}$

Using an in vitro assay of $^{45}$Ca release in fetal rat calvaria, UFH was found to stimulate bone resorption at concentrations commonly used for prophylaxis and treatment of the thromboembolism. $^{35}$ In contrast, >50-fold higher concentrations of the LMWH preparations enoxaparin, dalteparin, tinzaparin, and ardeparin than used clinically were required for an equivalent effect. Both molecular weight and sulfation are major determinants of $^{45}$Ca release by heparin, but affinity for AT-III is not an important factor. $^{35}$

Based on studies in animal models, we hypothesize that heparin binds to bone matrix and interacts with a variety of cell types found within the bone microenvironment, including cells of the osteoblast lineage. Such interactions may alter mesenchymal stem cell differentiation reducing the number of mature osteoblasts, $^{377}$ reduce collagen synthesis by osteoblasts, $^{36}$ and release specific growth factors and/or cytokines capable of inducing the formation of osteoclasts from pluripotent mononuclear precursors in the bone marrow.

**CONCLUSION**

LMWH preparations are at least as effective and safe as UFH and are more convenient. Although more expensive than UFH, the expense is likely to be offset by savings from reduced hospital stay. The major appealing feature of LMWH is the more predictable relationship between dose and response with LMWH than UFH, which translates to weight-adjusted dosing without laboratory monitoring.

The only study $^{300}$ that compared the predictability of the dose-response of LMWH to UFH demonstrated less variability with LMWH, but this was not abolished entirely. The efficacy and safety of LMWH might still be improved by monitoring antifactor Xa levels, but the anticipated improvement in clinical outcome is likely to be marginal and offset by inconvenience and expense. Weight-adjusted dosing could be misleading in patients with renal insufficiency or obesity, and further studies are required to determine whether monitoring is necessary in such cases. Based on current information, LMWH preparations should be administered in the majority of patients based on weight-adjusted dosing.

**RECOMMENDATIONS**

**Treatment of HIT (see Nonhemorrhagic Side Effects)**

1. We recommend the use of one of the following anticoagulant drugs to treat acute HIT complicated by thrombosis: danaparoid sodium (grade 1B), lepirudin (grade 1C), or argatroban (grade 1C).

2. We recommend that anticoagulation with one of these agents until the platelet count has recovered should also be considered for patients with acute HIT without thrombosis (isolated HIT), as there is a high risk for subsequent clinically evident thrombosis in these patients (all grade 2C in comparison to no treatment).

3. We recommend that clinicians do not use warfarin alone to treat acute HIT complicated by DVT because of the risk of causing venous limb gangrene (grade 1C).

4. Warfarin appears to be safe in acute HIT when it is given to a patient who is adequately anticoagulated with a drug that reduces thrombin generation in HIT, such as danaparoid, lepirudin, or argatroban, although it may be prudent to delay starting warfarin therapy until the platelet count has risen to >100 × 10⁹/L. We recommend that if warfarin is given to patients with acute HIT, it should be administered together with a drug that reduces thrombin generation in HIT, until the platelet count has recovered. Then, warfarin can be continued alone (grade 1C).

5. LMWH is contraindicated in HIT. We recommend that clinicians do not administer LMWH for the treatment of acute HIT (grade 1C+).

6. We recommend that clinicians do not administer prophylactic platelet transfusions for the treatment of acute HIT (grade 2C).

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