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Parenteral Anticoagulants*

American College of Chest Physicians
Evidence-Based Clinical Practice Guidelines
(8th Edition)

Jack Hirsh, MD, FCCP; Kenneth A. Bauer, MD; Maria B. Donati, MD, PhD; Michael Gould, MD, FCCP; Meyer M. Samama, MD; and Jeffrey I. Weitz, MD, FCCP

This chapter describes the pharmacology of approved parenteral anticoagulants, including the indirect anticoagulants, unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), fondaparinux, and danaparoid as well as the direct thrombin inhibitors hirudin, bivalirudin, and argatroban. UFH is a heterogeneous mixture of glycosaminoglycans that bind to antithrombin via a unique pentasaccharide sequence and catalyze the inactivation of thrombin factor Xa and other clotting factors. Heparin also binds to cells and other plasma proteins, endowing it with unpredictable pharmacokinetic and pharmacodynamic properties, and can lead to nonhemorrhagic side effects, such as heparin-induced thrombocytopenia (HIT) and osteoporosis. LMWHs have greater inhibitory activity against factor Xa than thrombin and exhibit less binding to cells and proteins than heparin. Consequently, LMWH preparations have more predictable pharmacokinetic and pharmacodynamic properties, have a longer half-life than heparin, and have a lower risk of nonhemorrhagic side effects. LMWHs can be administered once or twice daily by subcutaneous injection, without anticoagulant monitoring. Based on their greater convenience, LMWHs have replaced UFH for many clinical indications.

Fondaparinux, a synthetic pentasaccharide, catalyzes the inhibition of factor Xa, but not thrombin, in an antithrombin-dependent fashion. Fondaparinux binds only to antithrombin; therefore, HIT and osteoporosis are unlikely to occur. Fondaparinux has excellent bioavailability when administered subcutaneously, has a longer half-life than LMWHs, and is given once daily by subcutaneous injection in fixed doses, without anticoagulant monitoring. Three parenteral direct thrombin inhibitors and danaparoid are approved as alternatives to heparin in HIT patients.

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Key words: argatroban; bivalirudin; fondaparinux; hirudin; low-molecular-weight heparin; unfractionated heparin

Abbreviations: ACT = activated clotting time; APTT = activated partial thromboplastin time; AT = antithrombin; CrCl = creatinine clearance; HCII = heparin cofactor II; HIT = heparin-induced thrombocytopenia; INR = international normalized ratio; LMWH = low-molecular-weight heparin; PF4 = platelet factor 4; UFH = unfractionated heparin

Summary of Recommendations

2.2.3 Monitoring Antithrombotic Effect

2.2.3 In patients treated with LMWH, we recommend against routine coagulation monitoring (Grade 1C). In pregnant women treated with therapeutic doses of LMWH, we recommend monitoring of anti-Xa levels (Grade 1C).

2.2.4 Dosing and Monitoring in Special Situations

2.2.4 In obese patients given LMWH prophylaxis or treatment, we suggest weight-based dosing (Grade 2C). In patients with severe renal insufficiency (creatinine clearance [CrCl] < 30 mL/min) who require therapeutic anticoagulation, we suggest the use of UFH instead of LMWH (Grade 2C). If LMWH is used in patients with severe renal insuffi-
ciency (CrCl < 30 mL/min) who require therapeutic anticoagulation, we suggest using 50% of the recommended dose (Grade 2C).

3.0 Direct Thrombin Inhibitors

3.0 In patients who receive either lepirudin or desirudin and have renal insufficiency (CrCl < 60 mL/min but > 30 mL/min), we recommend that the dose be reduced and the drug be monitored using the activated partial thromboplastin time (Grade 1C). In patients with a CrCl < 30 mL/min, we recommend against the use of lepirudin or desirudin (Grade 1C). In patients who require anticoagulation and have previously received lepirudin or desirudin, we recommend against repeated use of these drugs because of the risk of anaphylaxis (Grade 1C).

3.1 Monitoring of Direct Thrombin Inhibitors

3.1 In patients receiving argatroban who are being transitioned to a vitamin K antagonist, we suggest that factor X levels measured using a chromogenic assay be used to adjust the dose of the vitamin K antagonist (Grade 2C).

This chapter focuses on parenteral anticoagulants in current use. These agents can be classified as indirect anticoagulants whose activity is mediated by plasma cofactors, and direct anticoagulants that do not require plasma cofactors to express their activity. The indirect parenteral anticoagulants in current use include heparin, low-molecular-weight heparins (LMWHs), fondaparinux, and danaparoid. These drugs have little or no intrinsic anticoagulant activity, and exert their anticoagulant activity by activating antithrombin (AT), an endogenous inhibitor of various activated clotting factors. The parenteral direct anticoagulants in current use all target thrombin. These agents include recombinant hirudins, bivalirudin, and argatroban.

2.0 Indirect Parenteral Anticoagulants

2.1 Heparin

About 90 years ago, McLean1 discovered that heparin has antithrombotic properties. Brinkhous et al2 then demonstrated that heparin is an indirect anticoagulant and requires a plasma cofactor to express its anticoagulant activity. Abildgaard3 subsequently identified this cofactor as ATIII in 1968, but it is now referred to as AT. The major anticoagulant action of heparin is mediated by the heparin/AT interaction. The mechanism of this interaction was elucidated in the 1970s.4–6 Heparin binds to lysine residues on AT, producing a conformational change at the arginine reactive center that converts AT from a slow, progressive thrombin inhibitor to a rapid inhibitor. The arginine reactive center on AT binds covalently to the active center serine of thrombin and other coagulation enzymes, thereby irreversibly inhibiting their procoagulant activity.5 Heparin then dissociates from AT and is reutilized (Fig 1).

Heparin binds to AT through a glucosamine unit4–7 contained within a unique pentasaccharide sequence.8 The development of LMWH in the 1980s introduced the concept that only heparin chains of sufficient length to bridge AT to thrombin potentiate thrombin inhibition. In contrast, heparin chains of any length that contain the high affinity pentasaccharide can catalyze factor Xa inhibition by AT. The AT-binding pentasaccharide has now been synthesized and developed into a drug called fondaparinux.9–12

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Figure 1. Inactivation of clotting enzymes by heparin. Top panel: ATIII is a slow inhibitor without heparin. Middle panel: Heparin binds to ATIII through a high-affinity pentasaccharide and induces a conformational change in ATIII, thereby converting ATIII from a slow inhibitor to a very rapid inhibitor. Bottom panel: ATIII binds covalently to the clotting enzyme, and the heparin dissociates from the complex and can be reutilized. Reprinted with permission from CHEST.
2.1.1 Structure and Mechanism of Action: Heparin is a highly sulfated mucopolysaccharide. It is heterogeneous with respect to molecular size, anticoagulant activity, and pharmacokinetic properties (Table 1). Heparin ranges in molecular weight from 3,000 to 30,000 with a mean of 15,000, which corresponds to approximately 45 saccharide units. Only about one third of the heparin molecules possess the unique pentasaccharide sequence, and it is this fraction that is responsible for most of the anticoagulant effect of heparin. Heparin chains that lack this pentasaccharide sequence have minimal anticoagulant activity when heparin is given in therapeutic concentrations. However, at concentrations higher than those usually administered clinically, heparin chains with or without the pentasaccharide sequence can catalyze thrombin inhibition by heparin cofactor II (HCII), a second plasma cofactor. At even higher concentrations, low-affinity heparin impairs factor Xa generation through AT- and HCII-independent mechanisms.

The heparin/AT complex inactivates thrombin (factor IIa) and factors Xa, IXa, XIa, and XIIa. Thrombin and factor Xa are most sensitive to inhibition by heparin/AT, and thrombin is about 10-fold more sensitive to inhibition than factor Xa. Heparin catalyzes AT-mediated thrombin inhibition by binding both to AT, via its pentasaccharide sequence, and to thrombin, in a nonspecific charge-dependent fashion, to form a ternary heparin/AT/thrombin complex. In contrast, to catalyze factor Xa inhibition by AT, heparin needs only to bind to AT via its high-affinity pentasaccharide.

Heparin chains consisting of < 18 saccharide units are too short to bridge thrombin and AT. Consequently, these chains are unable to catalyze thrombin inhibition. However, as long as they possess a pentasaccharide, short heparin chains can catalyze inhibition of factor Xa by AT. By inactivating thrombin or attenuating its generation, heparin not only prevents fibrin formation, but also inhibits thrombin-induced activation of platelets and factors V, VIII, and XI.

The interaction of heparin with HCII is charge dependent, but pentasaccharide-independent catalysis of HCII requires a higher concentration of heparin than that needed to promote thrombin inhibition by AT. The capacity of heparin capacity to activate HCII is also chain-length dependent with maximum catalysis, requiring heparin chains comprising a minimum of 24 saccharide units.

The third anticoagulant effect of heparin, which reflects AT- and HCII-independent modulation of factor Xa generation, is charge dependent and mediated by heparin binding to factor IXa. The effect is clinically unimportant because it requires doses of heparin considerably higher than those used therapeutically.

In vitro, heparin binds to platelets and, depending on the experimental conditions, can either induce or inhibit platelet aggregation. High-molecular-weight-heparin fractions with low affinity for AT have a greater effect on platelet function than LMWH fractions with high AT affinity. Heparin can prolong the bleeding time in humans and enhances blood loss from the microvasculature in rabbits. The interaction of heparin with platelets and endothelial cells may contribute to heparin-induced bleeding by mechanisms independent of its anticoagulant effect.

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**Table 1—Molecular Size, Anticoagulant Activity, and Pharmacokinetic Properties of Heparin**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Molecular size</td>
<td>Mean molecular weight, 15,000 (range, 3,000 to 30,000)</td>
</tr>
<tr>
<td>Anticoagulant activity</td>
<td>Only one third of heparin molecules contain the high-affinity pentasaccharide required for anticoagulant activity</td>
</tr>
<tr>
<td>Clearance</td>
<td>High-molecular-weight moieties are cleared more rapidly than low-molecular-weight moieties</td>
</tr>
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**Table 2—Anticoagulant Effects of Heparin**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Binds to AT and catalyzes the inactivation of thrombin and factors IIa, Xa, IXa, XIa, and XIIa</td>
<td>Major mechanism for anticoagulant effect, produced by only one third of heparin molecules (those containing the unique AT-binding pentasaccharide)</td>
</tr>
<tr>
<td>Binds to HCII and catalyzes inactivation of factor Ixa</td>
<td>Requires high concentrations of heparin and is independent of the pentasaccharide</td>
</tr>
<tr>
<td>Binds to factor IXa and inhibits factor X activation</td>
<td>Requires very high concentration of heparin and is AT and HCII independent</td>
</tr>
</tbody>
</table>

**Figure 2.** Molecular weight distributions of LMWHs and heparin. Reprinted with permission from CHEST.
In addition to its anticoagulant effects, heparin attenuates the proliferation of vascular smooth-muscle cells, inhibits osteoblast formation, and activates osteoclasts; these last two effects promote bone loss. Heparin-induced thrombocytopenia (HIT) is the most important nonhemorrhagic side effect of heparin, which is discussed by Warkentin et al. in a separate chapter.

2.1.2 Pharmacokinetics: Heparin is not absorbed orally and, therefore, must be administered parenterally. The two preferred routes of administration are by continuous IV infusion or subcutaneous injection. When the subcutaneous route is selected for delivery of treatment doses of heparin, the dose of heparin should be higher than the usual IV dose to overcome the reduced bioavailability associated with subcutaneous administration. If an immediate anticoagulant effect is required, the initial subcutaneous dose of heparin can be accompanied by an IV bolus injection.

Administration by subcutaneous injection in low doses of 5,000 U q12h, moderate doses of 12,500 U q12h, or larger doses of 15,000 U q12h reduces the plasma recovery of heparin. However, at high therapeutic doses (> 35,000 U/24 h), plasma recovery is almost complete.

After entering the blood stream, heparin binds to a number of plasma proteins, which reduces its anticoagulant activity. This phenomenon contributes to the variability of the anticoagulant response to heparin among patients with thromboembolic disorders and to the laboratory phenomenon of heparin resistance. Heparin also binds to endothelial cells and macrophages, a property that further complicates its pharmacokinetics. Binding of heparin to von Willebrand factor also inhibits von Willebrand factor-dependent platelet function.

Heparin is cleared through a combination of a rapid saturable and a much slower first-order mechanism. The saturable phase of heparin clearance is thought to be due to binding to endothelial cell receptors and macrophages. Bound heparin is internalized and depolymerized (Fig 4). The slower nonsaturable mechanism of clearance is largely renal. At therapeutic doses, a large proportion of heparin is cleared through the rapid saturable, dose-dependent mechanism. The complex kinetics of clearance renders the anticoagulant response to heparin nonlinear at therapeutic doses, with both the intensity and duration of effect rising disproportionately with increasing dose. Thus, the apparent biological half-life of heparin increases from approximately 30 min after an IV bolus of 25 U/kg, to 60 min with an IV bolus of 100 U/kg, to 150 min with a bolus of 400 U/kg.

2.1.3 Initial Dosing: The efficacy of heparin in the initial treatment of venous thromboembolism critically depends on dosage. Based on the results of randomized studies, patients assigned to lower starting doses of heparin had higher recurrence rates than those treated with higher doses. In the randomized study by Hull et al., patients with venous thrombosis were assigned to receive identical doses of heparin (an IV bolus of 5,000 U and 30,000 U/d), but one group received 15,000 U of heparin q12h by subcutaneous injection and the other 30,000 U of heparin per day by continuous IV infusion. Because of the reduced bioavailability of heparin after subcutaneous injection, patients assigned to the IV heparin regimen received substantially more heparin. The IV-administered heparin was more effective as evidenced by the observation that the activated partial thromboplastin time (APTT) was in the target range at 24 h in 71% of patients who received IV heparin, and in only 37% of those given subcutaneous heparin. Patients assigned to IV heparin had a significantly lower rate of recurrence than those given subcutaneous heparin.
Raschke et al\textsuperscript{52} randomized patients to receive heparin in fixed doses (5,000-U bolus followed by 1,000 U/h infusion) or adjusted doses using a weight-based nomogram (starting dose, 80 U/kg bolus followed by 18 U/kg/h infusion). Patients whose heparin was weight adjusted received higher doses within the first 24 h than those given fixed doses. The rate of recurrent thromboembolism was significantly lower with the weight-adjusted heparin regimen.

Initial dosing of IV heparin for venous thromboembolism is either weight-based (80 U/kg bolus and 1,000 U/h infusion)\textsuperscript{52} or administered as a bolus of 5,000 U followed by an infusion of at least 32,000 U/d.\textsuperscript{53} If heparin is given subcutaneously for treatment of venous thromboembolism, there are at least two options: (1) an initial IV bolus of approximately 5,000 U followed by 250 U/kg bid\textsuperscript{54}; or (2) an initial subcutaneous dose of 333 U/kg followed by 250 U/kg bid.\textsuperscript{55}

The doses of heparin recommended for treatment of acute coronary syndromes are lower than those used to treat venous thromboembolism. Thus, the American College of Cardiology\textsuperscript{56} recommends a heparin bolus of 60 to 70 U/kg (maximum 5,000 U) followed by an infusion of 12 to 15 U/kg/h (maximum 1,000 U/h) for unstable angina and non–ST-segment elevation myocardial infarction. Even lower doses of heparin are recommended\textsuperscript{57} when heparin is given in conjunction with fibrinolytic agents for treatment of ST-segment elevation myocardial infarction. Here, the bolus is about 60 U/kg (maximum 4,000 U), and the infusion is 12 U/kg/h (maximum of 1,000 U/kg/h).

2.1.4 Monitoring: The risk of heparin-associated bleeding increases with heparin dose\textsuperscript{58,59} and with concomitant administration of fibrinolytic agents\textsuperscript{60–63} or glycoprotein IIb/IIIa inhibitors.\textsuperscript{64,65} The risk of bleeding also is increased by recent surgery, trauma, invasive procedures, or concomitant hemostatic defects.\textsuperscript{66} Investigators have reported a relationship between the dose of heparin administered and both its efficacy\textsuperscript{37,50,67} and safety.\textsuperscript{64,65} Because the anticoagulant response to heparin varies among patients, it is standard practice to monitor heparin and to adjust the dose based on the results of coagulation tests. The evidence for adjusting the dose of heparin to maintain a therapeutic range is weak and based on a post hoc subgroup analysis of a descriptive study.\textsuperscript{68} In contrast, the evidence for maintaining the international normalized ratio (INR) within a therapeutic range in patients who are treated with vitamin K antagonists is strong because it is based on consistent results of randomized trials and case-control studies.

When given in therapeutic doses, the anticoagulant effect of heparin is usually monitored using the APTT. The activated clotting time (ACT) is used to monitor the higher heparin doses given to patients undergoing percutaneous coronary interventions or cardiopulmonary bypass surgery.

A retrospective study done in the 1970s suggested that an APTT ratio between 1.5 and 2.5 was associated with a reduced risk of recurrent venous thromboembolism.\textsuperscript{68} Based on this study, a therapeutic APTT range of 1.5 to 2.5 times control gained wide acceptance. The clinical relevance of this therapeutic range is uncertain because the validity of this range has not been confirmed by randomized trials and because the reagents and instruments used to measure the APTT have changed.\textsuperscript{69–78} Depending on the APTT reagent and the coagulometer used for the test, APTT results ranging from 48 to 108 s can be measured in samples with a heparin concentration of 0.3 U/mL, as determined using an anti-Xa assay.\textsuperscript{71,73} With heparin levels of 0.3 to 0.7 anti-Xa U/mL, modern APTT reagents and coagulometers produce APTT ratios that range from 1.6 to 2.7 times to 3.7 to 6.2 times control.\textsuperscript{69–74,76–83} Although various heparin dose-adjustment nomograms have been developed (Tables 3, 4\textsuperscript{53,67}), none is applicable to all APTT reagents.\textsuperscript{73} For these reasons, the therapeutic APTT range should be adapted to the responsiveness of the reagent and coagulometer used.\textsuperscript{69,72,74,75,77,78,80,82–85}

In the study that established a therapeutic range for the APTT,\textsuperscript{68} the APTT ratio of 1.5 to 2.5 corresponded to a heparin level of 0.2 to 0.4 U by protamine titration and a heparin level of 0.3 to 0.7 U

### Table 3—Protocol for Heparin Dose Adjustment

<table>
<thead>
<tr>
<th>APTT, s</th>
<th>Bolus Dose, U</th>
<th>Stop Infusion, mL/h at 40 U/mL (U per 24 h)</th>
<th>Time of Next Infusion, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>5,000</td>
<td>+ 3 (3.58)</td>
<td>6</td>
</tr>
<tr>
<td>50–59</td>
<td>5,000</td>
<td>- 3 (3.58)</td>
<td>6</td>
</tr>
<tr>
<td>60–85</td>
<td>0</td>
<td>0 (0)</td>
<td>Next morning</td>
</tr>
<tr>
<td>86–95</td>
<td>0</td>
<td>- 2 (3.84)</td>
<td>Next morning</td>
</tr>
<tr>
<td>96–120</td>
<td>30</td>
<td>- 2 (3.84)</td>
<td>6</td>
</tr>
<tr>
<td>&gt; 120</td>
<td>60</td>
<td>- 2 (3.84)</td>
<td>6</td>
</tr>
</tbody>
</table>

*Adapted from Cruickshank et al\textsuperscript{53}1991.
measured by an anti-Xa assay. Like APTT assays, anti-Xa assays vary in their responsiveness to heparin. Therefore, an appropriate anti-Xa assay should be selected for adjusting the APTT range. For treatment of venous thrombosis, it would be reasonable to select an APTT range that correlates with a heparin level of 0.3 to 0.7 U anti-Xa (or 0.2 to 0.4 U by protamine titration). The therapeutic range for coronary indications is unknown but is likely to correspond to heparin levels that are about 10% lower than used to treat patients with venous thromboembolism. The results of a randomized trial in patients with venous thromboembolism that showed that unmonitored weight-adjusted subcutaneous heparin given twice daily in high doses was as safe and effective as weight-adjusted LMWH challenges the need for APTT monitoring of heparin administered subcutaneously.

### 2.1.5 Heparin Resistance: Heparin resistance is a term used to describe the situation when patients require unusually high doses of heparin to achieve a therapeutic APTT. Several mechanisms explain heparin resistance, including AT deficiency, increased heparin clearance, elevations in heparin-binding proteins, and elevations in factor VIII and/or fibrinogen. Aprotinin and nitroglycerin may cause drug-induced heparin resistance, although the association with nitroglycerin is controversial. Elevated levels of factor VIII represent a common mechanism for apparent heparin resistance. Because elevated factor VIII levels shorten the APTT, there is a dissociation between the APTT and heparin levels measured by anti-Xa activity. In patients with venous thromboembolism who required large doses of heparin (>35,000 U/d), those randomized to heparin dosing based on anti-Xa levels (target range, 0.35 to 0.7 U/mL) had similar clinical outcomes and received lower doses of heparin than those randomized to dose adjustment based on APTT values. Given these results, it is reasonable to adjust heparin doses based on anti-Xa levels in patients with venous thromboembolism who require high doses of heparin to achieve a therapeutic APTT.

### 2.1.6 Limitations of Heparin: In addition to hemorrhagic complications, heparin has limitations based on its pharmacokinetic properties; its ability to induce immune-mediated platelet activation, which can lead to HIT (discussed in chapter on HIT by Warkentin et al); and its effect on bone metabolism, which can lead to osteoporosis. Other nonhemorrhagic side effects are very uncommon and include skin reactions that can progress to necrosis, alopecia, and hypersensitivity. Heparin therapy also can cause elevations of serum transaminases. This phenomenon is benign and not associated with liver disease.

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<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjustment</th>
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<tbody>
<tr>
<td>Initial dose</td>
<td>80 U/kg bolus, then change 18 U/kg/h</td>
</tr>
<tr>
<td>APTT, &lt; 35 s</td>
<td>80 U/kg bolus, then increase 4 U/kg/h</td>
</tr>
<tr>
<td>APTT, 35–45 s</td>
<td>40 U/kg bolus, then increase 2 U/kg/h</td>
</tr>
<tr>
<td>APTT, 46–70 s</td>
<td>No change</td>
</tr>
<tr>
<td>APTT, 71–90 s</td>
<td>Decrease infusion rate by 2 U/kg/h</td>
</tr>
<tr>
<td>APTT, &gt; 90 s</td>
<td>Hold infusion 1 h, then decrease infusion rate by 3 U/kg/h</td>
</tr>
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*Adapted from Raschke et al.†Therapeutic APTT range of 46 to 70 s corresponded to anti-Xa activity of 0.3 to 0.7 U/mL.

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Therefore, a patient receiving a continuous IV infusion of heparin at 1,250 U/h requires approximately 30 mg of protamine sulfate. Neutralization of subeutaneously administered heparin may require a prolonged infusion of protamine sulfate. The APTT can be used to assess the effectiveness of protamine sulfate neutralization of the anticoagulant effects of heparin.

The risk of severe adverse reactions to protamine sulfate, such as hypotension or bradycardia, can be minimized by administering the protamine slowly. Patients who have previously received protamine sulfate-containing insulin, have undergone vasectomy, or have known sensitivity to fish are at increased risk to have preformed antibodies against protamine sulfate and to suffer from allergic reactions, including anaphylaxis. Patients at risk for protamine sulfate allergy can be pretreated with corticosteroids and antihistamines.

A number of other substances or devices have been shown to neutralize the anticoagulant effects of unfractionated heparin (UFH). These include hexadimethrine (polybrene), heparinase (neutralase), PF4, extracorporeal heparin-removal devices, and synthetic protamine variants. None of these substances or devices are approved for clinical use.

2.2 LMWHs

LMWHs are derived from UFH by chemical or enzymatic depolymerization. LMWHs have reduced inhibitory activity against thrombin relative to factor Xa; have a more favorable benefit-to-risk ratio than heparin in animal models, and when used to treat venous thromboembolism, and have superior pharmacokinetic properties.

Structure and Mechanism of Action: LMWHs are about one third the molecular weight of UFH. They have a mean molecular weight of 4,000 to 5,000, which corresponds to about 15 saccharide units, and a molecular weight range of 2,000 to 9,000. Table 5 shows the various LMWHs approved for use in Europe, Canada, and the United States. Because they are prepared using different methods of depolymerization, the various LMWHs differ, at least to some extent, in their pharmacokinetic properties and anticoagulant profiles. Therefore, these drugs are not clinically interchangeable.

Depolymerization of heparin yields low-molecular-weight fragments that exhibit reduced binding to proteins and cells (Table 6). The reduced affinity for proteins and cells explains the anticoagulant, pharmacokinetic, and other biological differences between heparin and LMWH. Thus, compared with heparin, LMWHs have reduced ability to inactivate thrombin because the smaller fragments cannot bind simultaneously to AT and thrombin. Reduced binding to plasma proteins other than AT is responsible for the more predictable dose-response relationship of LMWHs. Decreased binding to macrophages and endothelial cells explains the longer plasma half-life of LMWH relative to UFH, whereas reduced binding to platelets and PF4 explains the lower incidence of HIT. Finally, the decreased binding of LMWH to osteoblasts results in less activation of osteoclasts and less bone loss.

Like heparin, 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. Because only pentasaccharide-containing heparin chains composed of at least 18 saccharide units are of sufficient length to bridge AT to thrombin, 50 to 75% of LMWH chains are too short to catalyze thrombin inhibition. However, these chains are capable of promoting factor Xa inactivation by AT because this reaction does not require bridging. Because virtually all molecules of UFH contain at

<table>
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<th>Table 5—Methods for Preparation of LMWHs and Danaparoid</th>
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<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>Dalteparin (Fragmin)</td>
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<tr>
<td>Danaparoid sodium (Orgaran)</td>
</tr>
<tr>
<td>Enoxaparin sodium (Lovenox/Clexane)</td>
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<tr>
<td>Nadroparin calcium (Fraxiparin)</td>
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<td>Tinzaparin (Innohep)</td>
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<table>
<thead>
<tr>
<th>Table 6—Biological Consequences of Reduced Binding of LMWH to Proteins and Cells</th>
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<tr>
<td><strong>Binding Target</strong></td>
</tr>
<tr>
<td>Thrombin</td>
</tr>
<tr>
<td>Proteins</td>
</tr>
<tr>
<td>Macrophages</td>
</tr>
<tr>
<td>Platelets</td>
</tr>
<tr>
<td>Osteoblasts</td>
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</table>
least 18 saccharide units, heparin has an anti-Xa-to-anti-IIa ratio of 1:1. In contrast, commercial LMWHs have anti-Xa-to-anti-IIa ratios between 2:1 and 4:1, depending on their molecular size distribution. At present, there is no evidence that the differences in anti-Xa-to-anti-IIa ratio among the LMWHs influence clinical outcomes, such as recurrent thrombosis or bleeding complications. Numerous randomized clinical trials have shown that LMWHs are safe and effective for the prevention and treatment of venous thromboembolism and for the treatment of non–ST-elevation acute coronary syndromes.

2.2.2 Pharmacokinetics: LMWHs have pharmacokinetic advantages over heparin; after subcutaneous injection, the bioavailability of LMWHs is about 90%, and LMWHs produce a more predictable anticoagulant response than heparin. The elimination half-life of LMWHs, which is 3 to 6 h after subcutaneous injection, is dose independent, and anti-Xa levels peak 3 to 5 h after dosing. One limitation of LMWHs is that they are cleared by the kidneys, so their biological half-life is prolonged in patients with renal failure.

2.2.3 Monitoring Antithrombotic Effect: LMWHs typically are administered in fixed or weight-adjusted doses for thromboprophylaxis and in weight-adjusted doses for therapeutic purposes. Laboratory monitoring is not generally necessary, but some authorities suggest that monitoring be done in obese patients and in patients with renal insufficiency. Monitoring also may be advisable when treatment doses of LMWH are given during pregnancy. If monitoring is required, the anti-Xa level is the recommended test.

Although some studies reported that high anti-Xa levels are associated with an increased bleeding risk, several other studies failed to show a relationship between anti-Xa levels and bleeding. A randomized controlled trial comparing monitored and unmonitored dalteparin therapy for treatment of venous thromboembolism showed no benefit of monitoring. Therefore, routine anti-Xa monitoring is not indicated.

For treatment of venous thromboembolism, a conservative peak anti-Xa level with twice-daily enoxaparin or nadroparin is 0.6 to 1.0 U/mL. The target range for peak anti-Xa levels (measured 4 h after dosing) with once-daily enoxaparin is likely to be > 1.0 U/mL whereas it is 0.85 U/mL with tinzaparin and 1.3 U/mL and 1.05 U/mL with nadroparin and dalteparin, respectively.

2.2.3 In patients treated with LMWH, we recommend against routine coagulation monitoring (Grade 1C). In pregnant women treated with therapeutic doses of LMWH, we recommend monitoring of anti-Xa levels (Grade 1C).

2.2.4 Dosing and Monitoring in Special Situations: With enoxaparin, anti-Xa activity is increased to appropriate levels when the drug is administered to obese patients in doses based on total body weight up to 144 kg. The same is true for dalteparin and tinzaparin in patients weighing up to 190 and 165 kg, respectively. In a metaanalysis, which included data on 921 patients with a BMI of 30, there was no excess in the rate of major bleeding over that observed in nonobese patients who received LMWH in doses adjusted by total body weight. For thromboprophylaxis with fixed-dose enoxaparin and nadroparin, there is a strong negative correlation between total body weight and anti-Xa levels in obese patients. Two small prospective trials have examined this issue in patients undergoing bariatric surgery, with inconclusive findings. The existing data, however, suggest that weight-based prophylactic dosing is preferable to fixed dosing for obese patients.

Appropriate dosing of LMWH in patients with severe renal insufficiency is uncertain. Contemporary randomized controlled trials evaluating LMWH efficacy and safety have generally excluded patients with severe renal insufficiency, defined in most studies as a creatinine clearance (CrCl) ≤ 30 mL/min. With few exceptions, pharmacokinetic studies have demonstrated that clearance of the anti-Xa effect of LMWH is highly correlated with CrCl. This was also observed in a large study of patients receiving therapeutic-dose enoxaparin for coronary indications, where a strong linear relationship was reported between CrCl and enoxaparin clearance (R = 0.85; p < 0.001). Of particular concern is the potential for accumulation of anti-Xa activity after multiple therapeutic doses. A linear correlation was shown between CrCl and anti-Xa levels (p < 0.0005) after multiple therapeutic doses of enoxaparin, with significantly increased anti-Xa levels in patients with a CrCl < 30 mL/min. Accumulation after multiple prophylactic doses appears to occur less frequently, but it is still observed. Thus, after multiple prophylactic doses of enoxaparin, anti-Xa clearance was reduced by 39%, and drug exposure (area under the curve of anti-Xa activity vs time) was 35% higher in patients with a CrCl < 30 mL/min compared with that in patients with a CrCl ≥ 30 mL/min. The data on accumulation with LMWHs other than
enoxaparin are limited. When used in full therapeutic doses, nadroparin clearance, but not tinzaparin clearance, was shown to be correlated with CrCl (R = 0.49; p < 0.002), even when the CrCl was as low as 20 mL/min. The apparent difference in tinzaparin clearance in patients with severe renal insufficiency may reflect its higher molecular weight relative to other LMWH preparations, which may result in clearance by hepatic rather than renal mechanisms.

Decreased LMWH clearance has been associated with increased bleeding risks in patients with severe renal insufficiency. In a recent metaanalysis, Lim et al compared the risk of major bleeding and anti-Xa levels in patients receiving LMWH who had severe renal insufficiency (CrCl ≤ 30 mL/min) with those in patients without renal impairment (CrCl > 30 mL/min). In 12 studies involving 4,971 patients given LMWH, the odds ratio (OR) for major bleeding was 2.25 (95% CI, 1.19 to 4.27) in patients with a CrCl ≤ 30 mL/min compared with that in those with a CrCl > 30 mL/min. Use of therapeutic-dose enoxaparin was associated with a further increase in major bleeding in patients with a CrCl ≤ 30 mL/min (8.3% vs 2.4%; OR 3.88; 95% CI, 1.78 to 8.45), but this was not observed when enoxaparin was empirically dose reduced (0.9% vs 1.9%; OR 0.58; 95% CI, 0.09 to 3.78). Based on these data, nondialysis-dependent patients with CrCl ≤ 30 mL/min who are treated with standard therapeutic doses of enoxaparin have an increased risk of major bleeding, and empiric dose reduction appears to reduce this risk. No conclusions could be made regarding other LMWHs because of limited data.

Increased bleeding also was found in a post-hoc analysis of data from the ESSENCE and TIMI 11B trials, where CrCl ≤ 30 mL/min was associated with an increased risk for major hemorrhage in patients receiving therapeutic doses of enoxaparin (RR = 6.1; 95% CI, 2.47–14.88; p = 0.0019). In another study of patients with either venous thromboembolism or acute coronary ischemia treated with therapeutic doses of enoxaparin or tinzaparin, a CrCl < 20 mL/min was associated with an RR of 2.8 (95% CI, 1.0 to 7.8) for bleeding complications. Finally, in a retrospective study of patients receiving multiple doses of enoxaparin, patients with renal insufficiency had an RR for any bleeding complication of 2.3 (p < 0.01) and an RR for major hemorrhage of 15.0 (p < 0.001).

In the setting of severe renal insufficiency where therapeutic anticoagulation is required, use of UFH avoids the problems associated with impaired clearance of LMWH preparations. Although there is no specific CrCl threshold at which the risk for accumulation becomes clinically significant, a CrCl of about 30 mL/min is a reasonable cutoff value based on the available literature. If LMWH is chosen, anti-Xa monitoring and/or dose reduction should be done to ensure that there is no accumulation. In the case of enoxaparin, dose reduction may be used in patients with CrCl < 30 mL/min. The recommended treatment dose of enoxaparin for patients with a CrCl < 30 mL/min who have acute coronary syndromes or venous thromboembolism is 50% of the usual dose (ie, 1 mg/kg once daily). No specific recommendations have been made for other LMWH preparations.

When given in prophylactic doses, LMWH has not been shown to increase the risk of bleeding complications, irrespective of the degree of impairment of renal function. Although higher anti-Xa levels were found in patients with renal failure who received repeated once-daily prophylactic doses of enoxaparin, the mean peak anti-Xa level was only 0.6 U/mL, and the trough was < 0.2 U/mL. No increased bleeding was observed. In a prospective cohort study of critically ill patients with a wide range of renal function, including some with acute renal failure who required hemodialysis, dalteparin bioaccumulation was not observed despite repeated dosing. The current recommendation for prophylactic dose enoxaparin in patients with a CrCl < 30 mL/min is 50% of the usual dose (ie, 30 mg once daily). No specific recommendations have been made for other LMWH preparations.

Recommendation

2.2.4 In obese patients given LMWH prophylaxis or treatment, we suggest weight-based dosing (Grade 2C). In patients with severe renal insufficiency (CrCl < 30 mL/min) who require therapeutic anticoagulation, we suggest the use of UFH instead of LMWH (Grade 2C). If LMWH is used in patients with severe renal insufficiency (CrCl < 30 mL/min) who require therapeutic anticoagulation, we suggest using 50% of the recommended dose (Grade 2C).

2.2.5 Reversing the Anticoagulant Effects of LMWH: There is no proven method for neutralizing LMWH. Studies in vitro and in animals have demonstrated that protamine sulfate neutralizes the anti-IIa activity of LMWH, thereby normalizing the APTT and the thrombin time. However, protamine sulfate neutralizes a variable portion of the anti-Xa activity of LMWH. It is likely that incomplete neutralization of anti-Xa activity reflects the fact that protamine does not bind to LMWH fragments within the LMWH preparations.
The clinical significance of incomplete anti-Xa neutralization of LMWH by protamine sulfate is unclear. In a small case series, protamine sulfate failed to correct clinical bleeding associated with LMWH in two of three patients, but there are no human studies that convincingly demonstrate or refute a beneficial effect of protamine sulfate on bleeding associated with the use of LMWH. One animal study reported a reduction in bleeding with protamine sulfate in a microvascular bleeding model, despite persistent anti-Xa activity. Another study demonstrated incomplete attenuation of bleeding.

A recent case report described the successful use of recombinant activated factor VII to control bleeding in a postoperative patient with renal failure who was receiving LMWH. In animal studies, synthetic protamine variants have been shown to be highly effective in neutralizing the anticoagulant effects of LMWH, including anti-Xa activity, and appear to be less toxic than protamine sulfate. Adenosine triphosphate completely reversed clinical bleeding related to LMWH in a rat model. These agents are not approved for clinical use.

The following approach is recommended in clinical situations where the anticoagulant effect of LMWH needs to be neutralized. If LMWH was given within 8 h, protamine sulfate should be administered in a dose of 1mg per 100 anti-Xa units of LMWH (1 mg enoxaparin equals approximately 100 anti-Xa units). A second dose of 0.5 mg protamine sulfate per 100 anti-Xa units should be administered if bleeding continues. Smaller doses of protamine sulfate can be given if the time since LMWH administration is longer than 8 h.

2.2.6 Nonhemorrhagic Complications: The frequency of HIT is threefold lower with LMWHs than with heparin, which reflects the fact that the interaction of heparin with PF4 is chain-length dependent. Although binding to PF4 is reduced, LMWHs can form complexes with PF4 that are capable of binding HIT antibodies. Consequently, in patients with HIT antibodies, there is cross-reactivity with LMWH (see chapter by Warkentin et al).

The risk of osteoporosis is lower with LMWH than with heparin. Likely, this reflects the lower affinity of LMWH for bone cells. Monreal et al compared the effects of heparin and LMWH on bone loss in rats and demonstrated that although both produced bone loss, the osteopenic effect was greater with heparin than with LMWH. In contrast, using different measures of bone loss, Mätzsch et al reported that with similar anti-factor Xa activities, the effects of LMWH and UFH on experimental bone loss were similar. Muir et al reported that heparin and LMWH both produced a dose-dependent decrease in cancellous bone volume in rats. However, the effects were greater with UFH than with LMWH. These investigators also showed that although both anticoagulants inhibited bone nodule formation and increased alkaline phosphatase in a dose-dependent manner, UFH had a six-fold greater effect than LMWH. Other investigators also reported that LMWH causes significant inhibition of osteoblast growth and produces osteopenic changes in rats.

Three small prospective clinical studies have reported on the effects of prophylactic doses of LMWH on bone density. The first was a cohort study in which 16 women receiving enoxaparin (40 mg/d) during pregnancy had serial bone density measurements of the proximal femur. Baseline measurements were taken within 2 weeks of starting therapy and then at 6 to 8 weeks and 6 months postpartum. Patients received enoxaparin for a mean duration of 25 weeks (range, 19 to 32 weeks). Compared with baseline values, there was no significant change in mean bone density at 6 weeks postpartum, and no patient experienced a >10% decrease in bone mass. At 6 months postpartum, there was a significant reduction in mean bone density (p = 0.02), and 2 of the 14 patients evaluated (14%) had a >10% decrease.

The second study was an open randomized trial that included 44 pregnant women with venous thromboembolism. Patients were assigned to either prophylactic doses of LMWH (dalteparin, n = 21) once daily subcutaneously or UFH (n = 23) twice daily subcutaneously during pregnancy and the puerperium. Dual radiograph absorptiometry of the lumbar spine was performed at 1, 6, 16, and 52 weeks. A healthy untreated control group was included for comparison. Mean bone density of the lumbar spine was significantly lower in the UFH group than in the dalteparin or control groups. Bone density measurements did not differ between the dalteparin and nonrandomized control groups.

The third clinical trial compared the effects of long-term treatment with LMWH and acenocoumarol on bone mineral density in 86 patients with venous thromboembolism. Treatment was given for 3 to 24 months. At 1 and 2 years of follow-up, the mean decrease in bone density of the femur was 1.8% and 2.6% in patients given acenocoumarol and 3.1% and 4.8% in patients given enoxaparin, respectively. These differences were not statistically significant. In summary, both UFH and LMWH preparations have the potential to produce osteopenia, but the risk is greater with UFH.

2.3 Fondaparinux

2.3.1 Discovery of the Natural High-Affinity Pentasaccharide: Building on the discovery of
Choay et al,8 who isolated heparin fragments with high affinity for AT, Choay et al8 and Thunberg et al180 demonstrated that the minimum heparin fragment necessary for high-affinity binding to AT consisted of a pentasaccharide. Choay et al181,182 then isolated this high-affinity pentasaccharide and demonstrated that it formed an equimolar complex with AT and enhanced AT-mediated inhibition of factor Xa. In 1987, Atha et al183 reported that both the 3-O- and 6-O-sulfated glucosamine residues within the pentasaccharide sequence were critical for its activity. These observations paved the way for the development of fondaparinux.

2.3.2 Pharmacology: A synthetic analog of the AT-binding pentasaccharide found in heparin and LMWH was prepared and its structure modified so as to increase its affinity for AT, thereby increasing its specific activity and half-life. The resulting synthetic pentasaccharide, fondaparinux, has a molecular weight of 1728. Its specific anti-Xa activity is higher than that of LMWH (about 700 U/mg and 100 U/mg, respectively), and its half-life after subcutaneous injection is longer than that of LMWH (17 h and ~4 h, respectively). The use of LMWH as the reference preparation for expressing the anti-Xa activity of fondaparinux is problematic.184,185 Fondaparinux binds to AT and produces a conformational change at the reactive site of AT that enhances its reactivity with factor Xa.186 AT then forms a covalent complex with factor Xa. Fondaparinux is released from AT and is available to activate additional AT molecules. Because it is too short to bridge AT to thrombin, fondaparinux does not increase the rate of thrombin inhibition by AT.

The pharmacokinetic properties and metabolism of fondaparinux have been studied in healthy volunteers.187,188 After subcutaneous injection, fondaparinux is rapidly and completely absorbed. A steady state is reached after the third or fourth once-daily dose, and fondaparinux is excreted unchanged in the urine. The terminal half-life is 17 h in young subjects and 21 h in elderly volunteers. Fondaparinux produces a predictable anticoagulant response and exhibits linear pharmacokinetics when given in subcutaneous doses of 2 to 8 mg or in IV doses ranging from 2 to 20 mg.188 There is minimal nonspecific binding of fondaparinux to plasma proteins other than AT, and most of the compound is bound to AT.189

Based on its excellent bioavailability after subcutaneous injection, lack of variability in anticoagulant response and long half-life, fondaparinux can be administered subcutaneously once daily in fixed doses without laboratory monitoring. Fondaparinux is contraindicated in patients with renal insufficiency (CrCl < 30 mL/min).

2.3.3 Dosing and Monitoring: Fondaparinux is given at a fixed dose of 2.5 mg for thromboprophylaxis. For treatment of deep vein thrombosis or pulmonary embolism, the drug is given at a dose of 7.5 mg for patients with a body weight of 50 to 100 kg; the dose is decreased to 5 mg for patients weighing < 50 kg and increased to 10 mg for those weighing > 100 kg. For patients with acute coronary syndromes, a once-daily fondaparinux dose of 2.5 mg is used.

Fondaparinux has not been monitored in clinical studies. Therefore, routine coagulation monitoring is not recommended. Some experts recommend a 50% reduction in the fondaparinux dose when the drug is given for thromboprophylaxis in patients with moderately severe renal insufficiency (i.e., CrCl < 50 mL/min).

Although coagulation monitoring is not recommended routinely, there may be circumstances when it is useful to determine the anticoagulant activity of fondaparinux. This can be measured using anti-Xa assays. To calculate drug levels, fondaparinux must be used as a reference standard in the assay. The therapeutic anti-Xa range for fondaparinux has not been established; however, when given at the 2.5-mg daily dose, levels of 0.2 to 0.4 µg/mL can be expected, whereas levels of 0.5 to 1.5 µg/mL are achieved with the 7.5-mg daily dose.

Fondaparinux does not bind to protamine sulfate, the antidote for heparin. If uncontrollable bleeding occurs with fondaparinux, recombinant factor VIIa may be effective.189

2.3.4 Nonhemorrhagic Side Effects: Fondaparinux has low affinity for PF4 and does not cross-react with HIT antibodies.189 There have been no reports of HIT with fondaparinux, and this agent has been used successfully to treat HIT patients.192

Heparin and LMWH can cause urticarial skin reactions. Rarely, skin necrosis can occur at injection sites. In these cases, HIT should be suspected. In a single-case report,193 fondaparinux was used successfully in a patient who developed skin reactions to three different LMWH preparations.

To date, studies on the effects of fondaparinux on bone metabolism have been limited to in vitro experiments using cultured osteoblasts. In one study, fondaparinux was compared with heparin, dalteparin, or enoxaparin. Osteoblasts exposed to fondaparinux showed significantly higher mitochondrial activity and protein synthesis than unexposed osteoblasts. In contrast, therapeutically relevant concentrations of heparin, dalteparin, or enoxaparin decreased matrix collagen type II content and calcification; fondaparinux had no effect on these measures of osteoblastic activity.194 A second study compared the effects of fondaparinux and dalteparin on human osteoblasts in culture. Dalteparin inhibited osteoblast
proliferation, protein synthesis, and the decreased levels of osteocalcin and alkaline phosphatase. In contrast, fondaparinux had no effect. Because of insufficient safety data, fondaparinux is contraindicated in pregnancy, although one pharmacologic study showed that there was no placental transfer of the pentasaccharide.

**Danaparoid Sodium**

Although it is a mixture of glycosaminoglycans (heparan sulfate, dermatan sulfate, and chondroitin sulfate), danaparoid acts as an anticoagulant primarily by catalyzing the inhibition of factor Xa in an AT-dependent fashion. The drug has low specific anti-Xa activity. Based on anti-Xa levels, danaparoid has a half-life of approximately 25 h.

Although danaparoid was shown to be effective for the prevention of venous thrombosis in high-risk patients, it is no longer marketed for this indication. Currently, its use is limited to the management of patients with HIT. Danaparoid is the only agent that has been evaluated for HIT in a randomized clinical trial, where it was reported to be significantly better than dextran. High success rates in the treatment of HIT also have been observed in retrospective studies. Danaparoid is approved for the treatment of HIT in some countries (eg, the Netherlands, Belgium, New Zealand) but not in the United States. Danaparoid does not prolong the INR, which facilitates monitoring when transitioning HIT patients from danaparoid to vitamin K antagonists. The long half-life of danaparoid is a disadvantage if patients require urgent surgery or invasive procedures. There is no antidote for danaparoid, which is problematic for patients who have serious bleeding.

### 3.0 Direct Thrombin Inhibitors

In contrast to indirect anticoagulants, which require a plasma cofactor to exert their activity, direct thrombin inhibitors have intrinsic activity because they bind to thrombin and block its enzymatic activity. The currently approved direct thrombin inhibitors are hirudin, bivalirudin, and argatroban.

**Hirudin**

A 65-amino acid polypeptide originally isolated from the salivary glands of the medicinal leech, *Hirudo medicinalis*, is now available in recombinant forms. Expressed in yeast, recombinant hirudins differ from native hirudin in that the Tyr residue at position 63 is not sulfated. Two recombinant forms of hirudin, known as lepirudin and desirudin, are currently approved for clinical use in North America and in Europe, respectively. Lepirudin is licensed for treatment of thrombosis complicating HIT, whereas desirudin is approved in Europe for postoperative thromboprophylaxis in patients undergoing elective hip arthroplasty.

Although there are minor differences in the amino-terminal composition of the two forms of recombinant hirudin, their mechanism of action and pharmacokinetic properties are identical. Both inhibit thrombin in a bivalent fashion. Thus, their globular amino-terminal domains interact with the active site of thrombin, whereas the anionic carboxy-terminal tails bind to exosite 1 on thrombin, the substrate-binding site. Both lepirudin and desirudin form high-affinity stoichiometric complexes with thrombin that are essentially irreversible.

**Dosing and Monitoring:** The recommended dose of IV lepirudin for HIT is 0.15 mg/kg/h, with or without an initial bolus of 0.4 mg/kg. The anticoagulant effect of lepirudin in this setting is monitored by using the APTT, and the dose is adjusted to achieve a target APTT ratio of 1.5 to 2.5.

When given for thromboprophylaxis after elective hip replacement surgery, desirudin is given subcutaneously at a dose of 15 mg twice daily. Routine APTT monitoring is unnecessary with this dose of desirudin.

The plasma half-life of the hirudins is 60 min after IV injection and 120 min after subcutaneous injection. Hirudin is cleared via the kidneys, and the drug accumulates in patients with renal insufficiency. The dose of hirudin must be reduced when the CrCl is < 60 mL/min and the drug is contraindicated in patients with renal failure.

Antibodies against hirudin develop in up to 40% of patients treated with lepirudin. Although most of these antibodies have no clinical impact, some can prolong the plasma half-life of lepirudin, resulting in drug accumulation. In addition, anaphylaxis can occur if patients with antibodies are reexposed to hirudin. Consequently, an alternative anticoagulant should be used in HIT patients who have previously been treated with hirudin.

**Bivalirudin:** A 20-amino acid synthetic polypeptide, bivalirudin is an analog of hirudin. The amino-terminal D-Phe-Pro-Arg-Pro sequence, which binds to the active site of thrombin, is connected via four Gly residues to a carboxy-terminal dodecapeptide that interacts with exosite 1 on thrombin. Like hirudin, bivalirudin forms a 1:1 stoichiometric complex with thrombin. However, once bound, thrombin cleaves the Pro-Arg bond within the amino terminal of bivalirudin, thereby allowing recovery of thrombin activity. Bivalirudin has a plasma half-life of 25 min after IV injection, and only 20% is excreted.
via the kidneys. Bivalirudin is licensed as an alternative to heparin in patients undergoing percutaneous coronary interventions. The currently recommended dose is a bolus of 0.7 mg/kg followed by an infusion of 1.75 mg/kg/h for the duration of the procedure. Bivalirudin is licensed as an alternative to heparin in HIT patients (with or without thrombosis) who require percutaneous coronary interventions. The drug also is being explored as an alternative to heparin in patients undergoing cardiopulmonary bypass surgery.

In contrast to hirudin, bivalirudin is not immunogenic. However, antibodies against hirudin can cross-react with bivalirudin in vitro. The clinical consequences of this cross-reactivity are uncertain.

**Argatroban:** A competitive inhibitor of thrombin, argatroban binds noncovalently to the active site of thrombin to form a reversible complex. The plasma half-life of argatroban is 45 min. It is metabolized in the liver via the cytochrome P450 3A4/5 enzyme system. Consequently, argatroban must be used with caution in patients with hepatic dysfunction. Because it is not renally excreted, however, argatroban is particularly useful in HIT patients with severe renal impairment.

Argatroban is licensed for treatment and prevention of HIT-associated thrombosis and for anticoagulation during percutaneous coronary interventions when heparin is contraindicated because of a recent history of HIT. Argatroban is given as a continuous IV infusion at a dose of 2 μg/kg/min, and the dose is adjusted to maintain the APTT ratio in the 1.5 to 3.0 range.

**3.0 In patients who receive either lepirudin or desirudin and have renal insufficiency (CrCl < 60 mL/min but > 30 mL/min), we recommend that the dose be reduced and the drug be monitored using the APTT (Grade 1C). In patients with a CrCl < 30 mL/min, we recommend against the use of lepirudin or desirudin (Grade 1C). In patients who require anticoagulation and have previously received lepirudin or desirudin, we recommend against repeated use of these drugs because of the risk of anaphylaxis (Grade 1C).**

**3.1 Monitoring of Direct Thrombin Inhibitors**

Although the APTT is used to monitor therapy with direct thrombin inhibitors, this test is not ideal. The dose response is not linear, and the APTT reaches a plateau with higher doses of the various drugs. In addition, APTT reagents vary in their sensitivities to direct thrombin inhibitors. The ecarin clotting time yields a more linear dose response, but this test is not widely available and has not been standardized.

All of the direct thrombin inhibitors increase the INR, albeit to a variable extent. When given in therapeutic doses, argatroban has the greatest effect on the INR. This phenomenon complicates transitioning from argatroban to vitamin K antagonists. To overcome this problem, the INR can be measured after stopping the argatroban infusion for several hours. Because holding argatroban may expose patients to a risk of thrombosis, another option is to monitor the vitamin K antagonist with a chromogenic factor X assay. In this setting, factor X levels < 45% have been associated with INR values > 2 when the effect of argatroban has been eliminated. Monitoring factor X levels may be safer than aiming for an INR of 4 or higher when vitamin K antagonists are given in conjunction with argatroban.

**Recommendation**

**3.1 In patients receiving argatroban who are being transitioned to a vitamin K antagonist, we suggest that factor X levels, measured using a chromogenic assay, be used to adjust the dose of the vitamin K antagonist (Grade 2C).**

**3.2 Reversal of Anticoagulant Effects**

There are no specific antidotes for direct thrombin inhibitors. Using inhibition of thrombin generation in shed blood as an index of activity, recombinant factor VIIa can reverse the anticoagulant effect of direct thrombin inhibitors in healthy volunteers. Although recombinant factor VIIa reduces bleeding induced by direct thrombin inhibitors in animals, the utility of this agent in patients has not been established.

Hemodialysis or hemoperfusion can remove bivalirudin or argatroban. Given their short half-lives, however, this is rarely necessary. Dialysis using special dialysis membranes can clear hirudin.

**Conflict of Interest Disclosures**

Dr. Hirsh discloses that he has received partial support for writing two books, one on Fondaparinux and one on low-molecular-weight heparin.

Dr. Bauer discloses that he received consultant fees from GlaxoSmithKline, Bayer Healthcare, Pfizer, Eisai, and Bristol-Myers Squibb. He is on the speakers bureau for GlaxoSmithKline and Sanofi-Aventis, and has assisted the advisory committees of...

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Bristol-Myers Squibb, Sanofi-Aventis, and SmithKline Beecham. Dr. Bauer discloses that he has received grant monies from Novo Nordisk, Sanofi, and Pfizer. He has received consultant fees from Pfizer. Dr. Samama has served on the speakers bureau of Boehringer Ingelheim and Sanofi, and has assisted advisory committees of BMS, AstraZeneca, Bayer, GlaxoSmithKline, and Mitsubishi.

Dr. Weitz discloses that he has received consultant fees from AstraZeneca, The Medicines Company, Schering-Plough, Bayer, Bristol-Myers Squibb, and Merck AG. He has served on an advisory committee for Eisai, Daiichi-Sankyo, Schering-Plough, and Mitsubishi.

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Dr. Weitz discloses that he has received consultant fees from AstraZeneca, The Medicines Company, Schering-Plough, Bayer, Bristol-Myers Squibb, and Merck AG. He has served on an advisory committee for Eisai, Daiichi-Sankyo, Schering-Plough, Bristol-Myers Squibb, Sanofi-Aventis, and SmithKline Beecham.

ADDENDUM

On page 153S, first column, second paragraph under Aragrotabon, the authors wish to add the following clarifying language:

Recommended Dosage for HIT/Heparin-Induced Thrombosis Thrombocytopenia Syndrome Patients Undergoing Percutaneous Coronary Interventions

For the initial dosage, an infusion of argatroban should be started at a concentration of 25 µg/kg/min, and a bolus of 350 µg/kg should be administered via a large-bore IV line over 3 to 5 min (see Table 9 from the argatroban prescribing information). The ACT should be checked 5 to 10 min after the bolus dose is completed. The procedure may proceed if the ACT is > 300 s.

Dosage Adjustment

If the ACT is < 300 s, an additional IV bolus dose of 150 µg/kg should be administered, the infusion dose should be increased to 30 µg/kg/min, and the ACT should be checked 5 to 10 min later (see Table 9 from the argatroban prescribing information). If the ACT is > 450 s, the infusion rate should be decreased to 15 µg/kg/min, and the ACT should be checked 5 to 10 min later (see Table 9 from the argatroban prescribing information). Once a therapeutic ACT (between 300 and 450 s) has been achieved, this infusion dose should be continued for the duration of the procedure.

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