This article focuses on parenteral anticoagulants in current use. These agents can be divided into 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 potentiating 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.

1.0 INDIRECT PARENTERAL ANTICOAGULANTS

1.1 Heparin

More than 90 years ago, McLean discovered that heparin has anticoagulant properties. Brinkhous and associates then demonstrated that heparin requires a plasma cofactor to express its anticoagulant activity.
In 1968, Abildgaard identified this cofactor as antithrombin III, which is now referred to as antithrombin. The major anticoagulant action of heparin is mediated by the heparin/AT interaction. The mechanism of this interaction was demonstrated in the 1970s. Heparin binds to positively charged residues on AT, producing a conformational change at the AT reactive center that converts AT from a slow inhibitor to a rapid inhibitor of serine proteases. 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. Heparin then dissociates from AT and is reused (Fig 1).

1.1.1 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 molecules range in molecular weight from 3,000 to 30,000 kDa with a mean of 15,000, which corresponds to approximately 45 saccharide units (Fig 2). 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 the 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 (Table 2). The heparin/AT complex inactivates thrombin (factor IIa) and factors Xa, IXa, XIa, and XIIa. Heparin catalyzes AT-mediated thrombin inhibition 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. In both cases binding occurs at the unique pentasaccharide sequence found within some heparin molecules. Heparin chains consisting of <18 saccharide units are too short to bridge AT to thrombin. Consequently, these chains are unable to catalyze thrombin inhibition. However, 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

| Table 1—Molecular Size, Anticoagulant Activity, and Pharmacokinetic Properties of Heparin |
|---------------------------------|------------------|
| Attribute                        | Characteristics  |
| Molecular size                   | Mean molecular weight, 15,000 kDa (range, 3,000-30,000) |
| Anticoagulant activity           | Only one-third of heparin molecules contain the high-affinity pentasaccharide required for anticoagulant activity |
| Clearance                        | High-molecular-weight moieties are cleared more rapidly than lower-molecular-weight moieties |
of HCII requires a higher concentration of heparin than that needed to promote thrombin inhibition by AT. Heparin’s capacity to activate HCII is also chain length-dependent, with maximum catalysis requiring heparin chains composed of a minimum of 24 saccharide units. Consequently, LMWHs are less effective at activating HCII than is heparin.

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 low-molecular-weight fractions with high AT affinity. Heparin can prolong the bleeding time in humans and it 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.

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. This is discussed by Linkins et al in this supplement.

### Table 2—Anticoagulant Effects of Heparin

<table>
<thead>
<tr>
<th>Effect</th>
<th>Comment</th>
</tr>
</thead>
<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 IIa</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>

AT = antithrombin; HCII = heparin cofactor II.

1.1.2 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 because subcutaneous administration is associated with reduced bioavailability. If an immediate anticoagulant effect is required, a higher initial subcutaneous dose of heparin can be administered. Alternatively, an IV bolus of heparin can be given in conjunction with the first subcutaneous dose.

Administration by subcutaneous injection in low doses (eg, 5,000 units q12h), moderate doses of 12,500 units q12h, or 15,000 units q12h reduces the plasma recovery of heparin. However, at high therapeutic doses (>35,000 units q24h) plasma recovery is almost complete.

After entering the bloodstream, heparin binds to a number of plasma proteins other than AT, reducing 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 believed to be due to binding to endothelial cell receptors and macrophages. Bound heparin is internalized and depolymerized. 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 render 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 bio logic half-life of heparin increases from approximately 30 min after an IV bolus of 25 units/kg, to 60 min with an IV bolus of 100 units/kg, to 150 min with a bolus of 400 units/kg.

1.1.3 Initial Dosing: The efficacy of heparin in the initial treatment of VTE is critically dependent 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 and associates, patients with venous thrombosis were
assigned to receive identical doses of heparin (an IV bolus of 5,000 units and 30,000 units per day), but one group received 15,000 units of heparin every 12 h by subcutaneous injection and the other 30,000 units of heparin per day by continuous IV infusion. Patients assigned to IV heparin had a significantly lower rate of recurrence than those given subcutaneous heparin, presumably as a result of reduced availability of the subcutaneously administered heparin. A study of 400 consecutive patients with acute pulmonary embolism further highlights the importance of early, aggressive therapy: Patients who achieved a therapeutic aPTT in <24 h also had lower in-hospital and 30-day mortality rates compared with those who did not.50

Raschke et al49 randomized patients to receive heparin in fixed doses (5,000-unit bolus followed by 1,000 units/h by infusion) or adjusted doses using a weight-based nomogram (starting dose, 80 units/kg bolus followed by 18 units/kg/h by infusion). Patients whose heparin was weight-adjusted received higher doses within the first 24 h than those given fixed doses of heparin. The rate of recurrent thromboembolism was significantly lower with the weight-adjusted heparin regimen.

Initial dosing of IV heparin for VTE is either weight-based (80 units/kg bolus and 18 units/kg/h infusion49) or administered as a bolus of 5,000 units followed by an infusion of at least 32,000 units/d.51 If heparin is given subcutaneously for treatment of VTE, there are at least two options: (1) an initial IV bolus of ~5,000 units followed by 250 units/kg twice daily52; or (2) an initial subcutaneous dose of 333 units/kg followed by 250 units/kg twice daily thereafter.35

The doses of heparin recommended for treatment of acute coronary syndromes are lower than those used to treat VTE. The American College of Cardiology recommends a heparin bolus of 60 to 70 units/kg (maximum 5,000 units) followed by an infusion of 12 to 15 units/kg/h (maximum 1,000 units/h) for unstable angina and non-ST-segment elevation myocardial infarction.53 Even lower doses of heparin are recommended when heparin is given in conjunction with fibrinolytic agents for treatment of ST-segment elevation myocardial infarction. Here, the bolus is about 60 units/kg (maximum 4,000 units) and the infusion is 12 units/kg/h (maximum of 1,000 units/h).54

1.1.4 Monitoring. The risk of heparin-associated bleeding increases with heparin dose55,56 and with concomitant administration of fibrinolytic agents57-60 or glycoprotein IIb/IIIa inhibitors.61,62 The risk of bleeding is also increased by recent surgery, trauma, invasive procedures, or concomitant hemostatic defects.63 In hospitalized patients, increasing number of comorbidities, age >60 y, supratherapeutic clotting times, and worsening hepatic dysfunction increase the risk of anticoagulant-associated bleeding.64

Investigators have reported a relationship between the dose of heparin administered and both its efficacy33,47,65 and safety.61,62 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 is based on a post hoc subgroup analysis of a descriptive study.66 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 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 VTE. 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 it has not been confirmed by randomized trials. Further, the measured response to the aPTT varies between reagents and instruments used to measure the aPTT. Depending on reagent and coagulometer, aPTT results ranging from 48 to 108 s can be measured in samples with a heparin concentration of 0.3 units/mL, as determined using an anti-Xa assay. With heparin levels of 0.3 to 0.7 anti-Xa units/mL, modern aPTT reagents and coagulometers produce aPTT ratios that range from 1.6-2.7 to 3.7-6.2 times control. Although various heparin dose-adjustment nomograms have been developed, none is applicable to all aPTT assays. For these reasons, the therapeutic aPTT range at a particular institution should be adapted to the responsiveness of the reagent and coagulometer used. In the study that established a therapeutic range for the aPTT, an aPTT ratio of 1.5 to 2.5 corresponded to a heparin level of 0.2 to 0.4 units by protamine titration and a heparin level of 0.3 to 0.7 units measured by an anti-Xa assay. Like aPTT assays, anti-Xa assays vary in their responsiveness to heparin; therefore, standardization of aPTT ratios by reference to anti-Xa levels is also problematic. Studies evaluating interlaboratory agreement in the monitoring of heparin have failed to show that correlating the aPTT with anti-Xa assays improves agreement between hospital laboratories, reflecting, at least in part, greater variation in the results of anti-Xa assays than in the aPTT results. Therefore, more research is needed to identify the optimal approach for monitoring unfractionated heparin (UFH) therapy. The therapeutic range of heparin for coronary indications is unknown, but is likely to correspond to heparin levels that are about 10% lower than those used for treatment of patients with VTE. The results of a randomized trial in patients with VTE that showed that unmonitored weight-adjusted subcutaneous heparin given twice daily in high doses was as safe and effective as unmonitored, weight-adjusted LMWH challenge the requirement for aPTT monitoring of heparin administered subcutaneously.

### 1.1.5 Heparin Resistance: Heparin resistance is a term used to describe the situation wherein 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 the levels of heparin-binding proteins, and high levels of factor VIII and/or fibrinogen. Aprotinin and nitroglycerin may cause drug-induced heparin resistance, although the association with nitroglycerin is controversial.

In patients with VTE who required large doses of heparin (> 35,000 units/d), patients randomized to heparin dosing based on anti-Xa levels (target range between 0.35-0.7 units/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 VTE who require very high doses of heparin to achieve a therapeutic aPTT.

### 1.1.6 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; 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 reactions. Although hypersensitivity reactions to heparin are uncommon, an unusually high number of adverse events with heparin were reported in North America in 2007. Typically, these events consisted of hypotension, nausea, and shortness of breath within 30 min of heparin administration. An investigation into this problem conducted by the US Centers for Disease Control identified the cause of these reactions to be a contaminant in heparin manufactured in China. The contaminant was an oversulfated chondroitin sulfate. It is postulated that

<table>
<thead>
<tr>
<th>Table 3—Example of a Heparin Dose Adjustment Nomogram</th>
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<tbody>
<tr>
<td><strong>Initial dose</strong></td>
</tr>
<tr>
<td><strong>aPTT, &lt; 35 s</strong></td>
</tr>
<tr>
<td><strong>aPTT, 35-45 s</strong></td>
</tr>
<tr>
<td><strong>aPTT, 46-70 s</strong></td>
</tr>
<tr>
<td><strong>aPTT, 71-90 s</strong></td>
</tr>
<tr>
<td><strong>aPTT, &gt; 90 s</strong></td>
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</tbody>
</table>

aPTT = activated partial thromboplastin time. (Adapted with permission from Raschke et al.)

*Therapeutic aPTT range of 46-70 s corresponded to anti-Xa activity of 0.3-0.7 units/mL. The target aPTT range in a particular institution should reflect what is known about the local reagents and equipment used to perform the assay.*
oversulfated chondroitin sulfate induces hypotension by promoting the activation of factor XII and the subsequent generation of bradykinin.95

Heparin therapy can also cause elevations of serum transaminases. The increase in transaminases is usually transient and is not associated with an increase in bilirubin; it is presumed to have no clinical consequences.96

The main nonhemorrhagic side effects of heparin are HIT and osteoporosis. HIT (discussed further by Linkins et al32 in this supplement) is caused by IgG subclass, heparin-dependent antibodies. These antibodies bind to a conformationally modified epitope on platelet factor 4 (PF4). Simultaneous binding of these antibodies to Fc receptors on the platelet surface causes platelet activation. Activated platelets shed highly prothrombotic microparticles and are then removed from the circulation causing thrombocytopenia. In addition, these activated platelets and microparticles provide a surface onto which coagulation factor complexes can assemble to promote thrombin generation. This phenomenon can then trigger venous or arterial thrombosis with venous thrombosis being more common.97 Osteoporosis is caused by binding of heparin to osteoblasts,32 which then release factors that activate osteoclasts in an interleukin 11-dependent fashion.98

1.1.7 Reversing the Anticoagulant Effect of Heparin: One advantage of heparin is that 1 IV protamine sulfate can rapidly reverse its anticoagulant effects. Protamine sulfate is a basic protein derived from fish sperm that binds to heparin to form a stable salt. One milligram of protamine sulfate will neutralize approximately 100 units of heparin. Therefore, a patient who bleeds immediately after receiving an IV bolus of 5,000 units of heparin should receive about 50 mg of protamine sulfate. Protamine sulfate is cleared from the circulation with a half-life of about 7 min. Because the half-life of IV heparin is 60 to 90 min when heparin is given as an IV infusion, only heparin given during the preceding several hours needs to be considered when calculating the dose of protamine sulfate that needs to be administered. Therefore, a patient receiving a continuous IV infusion of heparin at 1,250 units/h requires approximately 30 mg of protamine sulfate to neutralize the heparin that was given in the past 2 to 2.5 h. Neutralization of subcutaneously 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.99

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.100,101 Such reactions are uncommon, but if there is concern about a potential protamine sulfate allergy, patients can be pretreated with corticosteroids and antihistamines.

A number of other substances or devices have been shown to neutralize the anticoagulant effects of UFH. These include hexadimethrine (Polybrene),102,103 heparinase (Neutralase),104 PF4,105,106 extracorporeal heparin removal devices,107 and synthetic protamine variants.108 None of these is approved for clinical use.

1.2 Low-Molecular-Weight Heparins

LMWHs are derived from UFH by chemical or enzymatic depolymerization. LMWHs have reduced inhibitory activity against thrombin relative to factor Xa,9,10,109-111 have a more favorable benefit-to-risk ratio than heparin in animal models112,113 and when used to treat VTE,114 and have superior pharmacokinetic properties.115-121

1.2.1 Structure and Mechanism of Action: LMWHs are about one-third the molecular weight of UFH. LMWHs have a mean molecular weight of 4,000 to 5,000—which corresponds to about 15 saccharide units—and a range of 2,000 to 9,000. Table 4 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 and in their recommended dosing regimens. Therefore, these drugs are not interchangeable on a unit-for-unit basis.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Method of Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Becapararin</td>
<td>Alkaline degradation</td>
</tr>
<tr>
<td>Dalteparin (Fragmin)</td>
<td>Nitrous acid depolymerization</td>
</tr>
<tr>
<td>Danaparoid sodium</td>
<td>Prepared from animal gut mucosa; contains heparan sulfate (84%), dermatan sulfate (12%), and chondroitin sulfate (4%)</td>
</tr>
<tr>
<td>(Orgaran)</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin sodium</td>
<td>Benzylization followed by alkaline depolymerization</td>
</tr>
<tr>
<td>(Lovenox/Clexane)</td>
<td></td>
</tr>
<tr>
<td>Nadroparin calcium</td>
<td>Nitrous acid depolymerization</td>
</tr>
<tr>
<td>(Fraxiparin)</td>
<td></td>
</tr>
<tr>
<td>Tinzaparin (Innohep)</td>
<td>Enzymatic depolymerization with heparinase</td>
</tr>
</tbody>
</table>

LMWH = low-molecular-weight heparin.
plasma proteins other than AT is responsible for because the smaller fragments cannot bind simultaneously. LMWHs have reduced ability to inactivate thrombin compared with heparin, macokinetic, and other biologic differences between proteins and cells (Table 5). The reduced affinity for weight fragments that exhibit reduced binding to endothelial cells explains the longer plasma half-life of UFH 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 catalyzing AT-mediated inhibition of coagulation factors. The pentasaccharide sequence required for binding is 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 least 18 saccharide units, heparin has, by definition, 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 VTE and for the treatment of non-ST-elevation acute coronary syndromes.

### 1.2.2 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 predominately cleared by the kidneys so their biologic half-life may be prolonged in patients with renal failure.

### 1.2.3 Monitoring Antithrombotic Effect

LMWHs are typically administered in fixed or weight-adjusted doses for thromboprophylaxis and in weight-adjusted doses for therapeutic purposes. Coagulation monitoring is not generally necessary, but some authorities suggest that monitoring be done in obese patients and in those with renal insufficiency. Monitoring may also be advisable when treatment doses of LMWH are given during pregnancy.

Although some studies reported that high anti-Xa levels were 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 VTE showed no benefit of monitoring. Monitoring is thus not recommended for the majority of patients; if monitoring is required, the anti-Xa level is the recommended test.

For treatment of VTE, a conservative peak anti-Xa level with twice-daily enoxaparin or nadroparin is 0.6 to 1.0 units/mL. The target range for peak anti-Xa levels (measured 4 h after dosing) with once-daily enoxaparin is likely to be above 1.0 units/mL, whereas it is 0.85 units/mL with tinzaparin and 1.3 units/mL and 1.05 units/mL with nadroparin and dalteparin, respectively. The suggested peak target ranges for several LMWHs are shown in Table 6.

### 1.2.4 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 a weight of 144 kg. The same is true for dalteparin and tinzaparin in patients weighing up to 190 and 165 kg, respectively. In a meta-analysis that included data on 921 patients with a BMI ≥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.\textsuperscript{145} 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.\textsuperscript{146-148} Several small prospective trials have examined this issue in patients undergoing bariatric surgery, with inconclusive findings.\textsuperscript{149-152}

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) \( \leq 30 \) mL/min. With few exceptions,\textsuperscript{153} pharmacokinetic studies have demonstrated that clearance of the anti-Xa effect of LMWH is highly correlated with CrCl.\textsuperscript{154} This was also observed in a large study of patients receiving therapeutic-dose enoxaparin for coronary indications, in which a strong linear relationship was reported between CrCl and enoxaparin clearance (\( R = 0.85, P < .001 \)).\textsuperscript{141} 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 (\( P < .0005 \)) after multiple therapeutic doses of enoxaparin, with significantly increased anti-Xa levels in patients with a CrCl \( < 30 \) mL/min.\textsuperscript{155} 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 \( \geq 30 \) mL/min.\textsuperscript{156} The data on accumulation with LMWHs other than enoxaparin is limited. Although the amount of published evidence is limited, bioaccumulation of dalteparin has been reported in patients with significant renal insufficiency who receive therapeutic doses of dalteparin.\textsuperscript{157} When used in full therapeutic doses, nadroparin clearance, but not tinzaparin clearance, was shown to be correlated with CrCl (\( R = 0.49, P < .002 \)).\textsuperscript{158} even when the CrCl was as low as 20 mL/min.\textsuperscript{159} The apparent difference in tinzaparin clearance in patients with severe renal insufficiency may reflect metabolism by hepatic mechanisms, possibly due to the higher molecular weight of tinzaparin compared with other LMWHs.

Decreased LMWH clearance has been associated with increased bleeding risks in patients with severe renal insufficiency. Lim and associates\textsuperscript{160} compared the risk of major bleeding and anti-Xa levels in patients receiving LMWH who had severe renal insufficiency (CrCl \( \leq 30 \) mL/min) with those in patients without renal impairment (CrCl \( > 30 \) mL/min). In 12 studies involving 4,971 patients given LMWH, the OR for major bleeding was 2.25 (95\% CI, 1.19-4.27) in patients with a CrCl \( \leq 30 \) mL/min compared with that in those with a CrCl \( > 30 \) mL/min. Enoxaparin at a therapeutic dose was associated with a further increase in major bleeding in patients with a CrCl \( \leq 30 \) mL/min (8.3\% vs 2.4\%; OR, 3.85; 95\% CI, 1.78-8.45), but this was not observed when enoxaparin was empirically dose reduced (0.9\% vs 1.9\%; OR, 0.58; 95\% CI, 0.09-3.78). Based on these data, nondialysis-dependent patients with CrCl \( \leq 30 \) mL/min who are treated with standard therapeutic doses of enoxaparin have an increased risk of major bleeding, and empirical dose reduction appears to reduce this risk. No conclusions could be made regarding other LMWHs because of limited data.

Increased bleeding was also found in a post hoc analysis of data from the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) and Thrombolysis in Myocardial Infarction (TIMI) 11B trials, in which CrCl \( \leq 30 \) mL/min was associated with an increased risk for major hemorrhage in patients receiving therapeutic doses of enoxaparin (relative risk [RR] = 6.1; 95\% CI, 2.47-14.88; \( P = .0019 \)).\textsuperscript{161} In another study in patients with either VTE or acute coronary ischemia treated with therapeutic doses of enoxaparin or tinzaparin, a CrCl \( < 20 \) mL/min was associated with a RR of 2.8 (95\% CI, 1.0-7.8) for bleeding complications.\textsuperscript{162} 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 (\( P < .01 \)) and an RR for major hemorrhage of 15.0 (\( P < .001 \)).\textsuperscript{163}

In the setting of severe renal insufficiency in which 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 LMWH accumulation becomes clinically significant, an estimated CrCl of about 30 mL/min is a reasonable cutoff value based on the available literature. If LMWH is chosen for patients with an estimated creatinine clearance of < 30 mL/min, anti-Xa monitoring
and/or dose reduction should be considered 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 VTE 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 units/mL, the trough was < 0.2 units/mL, and 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. In a more recent study, subcutaneous dalteparin (5,000 International Units) was given daily to consecutive ICU patients who had an estimated creatinine clearance < 30 mL/min. There was no evidence of drug accumulation nor was the risk of bleeding increased. For patients with a CrCl < 30 mL/min who require pharmacologic VTE prophylaxis, manufacturer of enoxaparin recommends that 30 mg once daily be used. In a small comparative study of enoxaparin (40 mg once daily) or tinzaparin (4,500 units once daily), bioaccumulation of enoxaparin, but not tinzaparin, was seen over 8 days of exposure. For other LMWHs, dosing recommendations cannot be made in the setting of renal insufficiency.

1.2.5 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 that have low sulfate charge density.

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 LMWH-induced bleeding.

A single case report describes 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 LMWH-induced bleeding related to LMWH in a rat model, as did PMX 60056, a salicylamide-derived heparin antagonist. In vitro experiments suggest that an antithrombin variant (AT-N135Q-Pro394) may neutralize the anticoagulant effects of heparin derivatives, including LMWH and fondaparinux. These agents are not approved for clinical use.

The following approach is recommended in clinical situations in which 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 1 mg per 100 anti-Xa units of LMWH up to a maximum single dose of 50 mg (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.

1.2.6 Nonhemorrhagic Complications: The frequency of HIT is threefold lower with LMWHs than with heparin. This 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 (Linkins et al.).

The risk of osteoporosis is lower with LMWH than with heparin. Likely, this reflects the lower affinity of LMWH for osteoclasts and osteoblasts. Monreal and associates 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 LMWH. In contrast, using different measures of bone loss, Mätzsch and associates reported that, at similar anti-factor Xa activities, the effects of LMWH and UFH on experimental bone loss were similar. Shaughnessy and colleagues 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 sixfold 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 daily) 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, 19-32 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 = .02) and two of the 14 patients evaluated (14%) had a >10% decrease.

The second study was an open randomized trial that included 44 pregnant women with VTE. 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 x-ray absorptiometry of the lumbosacral 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 control groups.

The third clinical trial compared the effects of long-term treatment with LMWH (enoxaparin) and acenocoumarol on bone mineral density in 86 patients with VTE. 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.

A recent review confirms that the strength of the association between LMWH and osteoporosis remains unclear.

In summary, both UFH and LMWH preparations have the potential to produce osteopenia. The risk is lower with LMWH.

1.3 Fondaparinux

1.3.1 Discovery of the Natural High-Affinity Pentasaccharide: Building on the discovery of Lindahl and associates, who isolated heparin fragments with high affinity for AT, Choay and colleagues 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 and associates 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.

1.3.2 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 its half-life. The resulting synthetic pentasaccharide, fondaparinux, has a molecular weight of 1,728. Its specific anti-Xa activity is higher than that of LMWH (about 700 units/mg and 100 units/mg, respectively), and its half-life after subcutaneous injection is longer than that of LMWH (17 h and about 4 h, respectively). The use of LMWH as the reference preparation for determining the measured anti-Xa activity of fondaparinux is problematic. As a result, fondaparinux levels should only be determined using assays that use known fondaparinux concentrations to generate their standard curve.

Fondaparinux binds to AT and produces a conformational change at the reactive site of AT that enhances its reactivity with factor Xa. 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. 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 pharmakokinetics when given in subcutaneous doses of 2 to 8 mg or in IV doses ranging from 2 to 20 mg. There is minimal nonspecific binding of fondaparinux.
thromboprophylaxis, the dose of fondaparinux should be reduced by 50% or low-dose heparin should be used in place of fondaparinux.

Fondaparinux has not been monitored in clinical studies. Therefore, routine coagulation monitoring is not recommended. In patients with moderate renal insufficiency (ie, CrCl 30-50 mL/min) who require thromboprophylaxis, the dose of fondaparinux should be reduced by 50% or low-dose heparin should be used in place of fondaparinux.

Although coagulation monitoring is not recommended on a routine basis, there may be circumstances in which it is useful to determine the anticoagulant activity of fondaparinux. This can be measured using fondaparinux-specific anti-Xa assays. The therapeutic anti-Xa range for fondaparinux has not been established. However, when given at the 2.5 mg daily dose, the peak steady-state plasma concentration is, on average, 0.39 to 0.50 mg/L and is reached approximately 3 h post dose. For patients receiving therapeutic doses of fondaparinux (eg, 7.5 mg daily for an individual of average body weight), the mean peak steady-state plasma concentration can be expected to be 1.20 to 1.26 mg/L 3 h post dose.

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

1.3.4 Nonhemorrhagic Side Effects: Fondaparinux has low affinity for PF4 and does not cross-react with HIT antibodies. Although there have been isolated case reports of HIT associated with the use of fondaparinux and reports of HIT antibodies without thrombocytopenia in patients given prophylaxis with fondaparinux, numerous case reports and case series suggest that this agent can be used to treat patients with HIT. This issue is further discussed in the article on HIT by Linkins et al in this supplement and has been summarized by Blackmer et al.

Heparin and LMWH can cause urticarial skin reactions. Rarely, skin necrosis can occur at sites of injection. In these cases, HIT should be suspected. In a single case report, 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 2 content and calcification; fondaparinux had no effect on these measures of osteoblastic activity. 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 not widely used in pregnancy. Although one pharmacologic study showed that there was no placental transfer of the pentasaccharide, low levels of anti-Xa activity were detected in the umbilical cord blood in newborns of mothers treated with fondaparinux.

1.4 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; it is discussed in greater detail in the article on HIT in this supplement. Danaparoid is the only agent that has been evaluated for HIT in a randomized clinical trial, wherein it was reported to be significantly better than dextran. High success rates in the treatment of HIT have also 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. This facilitates monitoring when transitioning patients with
HIT from danaparoid to vitamin K antagonists. The long half-life of danaparoid is a disadvantage if patients require urgent surgery or invasive procedures. It also is problematic if patients have serious bleeding because there is no antidote for danaparoid.

2.0 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, hirudin 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 and the United States for postoperative thromboprophylaxis in patients undergoing elective hip arthroplasty.

Although there are minor differences in the aminoterminal 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 aminoterminal 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 1:1 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 times control (Linkins et al.). When given for thromboprophylaxis after elective hip replacement surgery, desirudin is given subcutaneously at a dose of 15 mg twice daily without monitoring.

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 rapidly 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. In a retrospective observational analysis of 181 patients with confirmed HIT who were treated with lepirudin at a mean dose of 0.06 mg/kg/h for a median treatment duration of 7.7 days, 13.8% suffered a thrombotic event and 20.4% suffered major hemorrhage. The mean aPTT ratio was > 1.5 in > 99% of patients.

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 re-exposed to hirudin. Consequently, an alternative anticoagulant should be considered in patients with HIT 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 interventions for unstable angina or non-ST-elevation or ST-elevation myocardial infarction and in patients with HIT (with or without thrombosis) who require percutaneous coronary interventions. The currently recommended dose is a bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h for the duration of the procedure. Dose reduction should be considered in patients with moderate to severe renal impairment. The drug has also been 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

Argatroban is a small molecule competitive inhibitor of thrombin (molecular weight, 500 kDa). It
binds noncovalently to the active site of thrombin to form a reversible complex.\textsuperscript{224-226} The plasma half-life of argatroban is 45 min. It is metabolized in the liver\textsuperscript{226} 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 patients with HIT 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 with an initial dose of 1 to 2 \( \mu \)g/kg/min and the dose is adjusted to maintain the aPTT ratio in the 1.5 to 2.5 range (Linkins et al.).\textsuperscript{32}

### 2.1 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.\textsuperscript{227} 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.\textsuperscript{229} Monitoring factor X levels may be safer than aiming for an INR \( \geq \) 4 when vitamin K antagonists are given in conjunction with argatroban.\textsuperscript{229,230}

### 2.2 Reversal of Anticoagulant Effects

There are no specific antidotes for direct thrombin inhibitors. Using inhibition of thrombin generation in whole blood recovered from a bleeding time incision as an index of activity, recombinant factor VIIa can reverse the anticoagulant effect of direct thrombin inhibitors in healthy volunteers.\textsuperscript{231} Although recombinant factor VIIa reduces bleeding induced by direct thrombin inhibitors in animals, the usefulness of this agent in patients who are bleeding has not been established.

Hemodialysis or hemoperfusion can remove bivalirudin or argatroban. Dialysis using “high-flux” dialysis membranes can clear hirudin.

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### REFERENCES


