150–200 units/kg is given if the drug is administered once daily. If a twice-daily regimen is used, a dose of 100 units/kg is given. In patients with unstable angina, LMWH is given SC on a twice-daily basis at a dose of 100–120 units/kg.

SIDE EFFECTS The major complication of LMWH is bleeding. Meta-analyses suggest that the risk of major bleeding is lower with LMWH than with unfractionated heparin. HIT and osteoporosis are less common with LMWH than with unfractionated heparin.

Bleeding Like the situation with heparin, bleeding with LMWH is more common in patients receiving concomitant therapy with antiplatelet or fibrinolytic drugs. Recent surgery, trauma, or underlying hemostatic defects also increase the risk of bleeding with LMWH.

Although protamine sulfate can be used as an antidote for LMWH, protamine sulfate incompletely neutralizes the anticoagulant activity of LMWH because it only binds the longer chains of LMWH. Because longer chains are responsible for catalysis of thrombin inhibition by antithrombin, protamine sulfate completely reverses the anti-factor IIa activity of LMWH. In contrast, protamine sulfate only partially reverses the anti-factor Xa activity of LMWH because the shorter pentasaccharide-containing chains of LMWH do not bind to protamine sulfate. Consequently, patients at high risk for bleeding may be more safely treated with continuous IV unfractionated heparin than with SC LMWH.

Thrombocytopenia The risk of HIT is about fivefold lower with LMWH than with heparin. LMWH binds less avidly to platelets and causes less PF4 release. Furthermore, with lower affinity for PF4 than heparin, LMWH is less likely to induce the conformational changes in PF4 that trigger the formation of HIT antibodies.

LMWH should not be used to treat HIT patients because most HIT antibodies exhibit cross-reactivity with LMWH. This in vitro cross-reactivity is not simply a laboratory phenomenon because there are case reports of thrombosis when HIT patients were switched from heparin to LMWH.

Osteoporosis Because the risk of osteoporosis is lower with LMWH than with heparin, LMWH is the better choice for extended treatment.

Fondaparinux A synthetic analogue of the antithrombin-binding pentasaccharide sequence, fondaparinux differs from LMWH in several ways (Table 143-6). Fondaparinux is licensed for thromboprophylaxis in general medical or surgical patients and in high-risk orthopedic patients and as an alternative to heparin or LMWH for initial treatment of patients with established venous thromboembolism. Although widely used in Europe, as an alternative to heparin or LMWH in patients with acute coronary syndromes, fondaparinux is not licensed for this indication in the United States.

MECHANISM OF ACTION As a synthetic analogue of the antithrombin-binding pentasaccharide sequence found in heparin and LMWH, fondaparinux has a molecular weight of 1728. Fondaparinux binds only to antithrombin (Fig. 143-5) and is too short to bridge thrombin to antithrombin. Consequently, fondaparinux catalyzes factor Xa inhibition by antithrombin and does not enhance the rate of thrombin inhibition.

TABLE 143-6 COMPARISON OF LMWH AND FONDAPARINUX

Features	LMWH	Fondaparinux
Number of saccharide units	15–17	5
Catalysis of factor Xa inhibition	Yes	Yes
Catalysis of thrombin inhibition	Yes	No
Bioavailability after subcutaneous administration (%)	90	100
Plasma half-life (h)	4	17
Renal excretion	Yes	Yes
Induces release of tissue factor pathway inhibitor	Yes	No
Neutralized by protamine sulfate	Partially	No

PHARMACOLOGY Fondaparinux exhibits complete bioavailability after SC injection. With no binding to endothelial cells or plasma proteins, the clearance of fondaparinux is dose independent and its plasma half-life is 17 h. The drug is given SC once daily. Because fondaparinux is cleared unchanged via the kidneys, it is contraindicated in patients with a creatinine clearance <30 mL/min and should be used with caution in those with a creatinine clearance <50 mL/min.

Fondaparinux produces a predictable anticoagulant response after administration in fixed doses because it does not bind to plasma proteins. The drug is given at a dose of 2.5 mg once daily for prevention of venous thromboembolism. For initial treatment of established venous thromboembolism, fondaparinux is given at a dose of 7.5 mg once daily. The dose can be reduced to 5 mg once daily for those weighing <50 kg and increased to 10 mg for those >100 kg. When given in these doses, fondaparinux is as effective as heparin or LMWH for initial treatment of patients with DVT or PE and produces similar rates of bleeding.

Fondaparinux is used at a dose of 2.5 mg once daily in patients with acute coronary syndromes. When this prophylactic dose of fondaparinux was compared with treatment doses of enoxaparin in patients with non-ST-segment elevation acute coronary syndrome, there was no difference in the rate of cardiovascular death, MI, or stroke at 9 days. However, the rate of major bleeding was 50% lower with fondaparinux than with enoxaparin, a difference that likely reflects the fact that the dose of fondaparinux was lower than that of enoxaparin. In acute coronary syndrome patients who require percutaneous coronary intervention, there is a risk of catheter thrombosis with fondaparinux unless adjunctive heparin is given.

SIDE EFFECTS Fondaparinux does not cause HIT because it does not bind to PF4. In contrast to LMWH, there is no cross-reactivity of fondaparinux with HIT antibodies. Consequently, fondaparinux appears to be effective for treatment of HIT patients, although large clinical trials supporting its use are lacking.

The major side effect of fondaparinux is bleeding. There is no antidote for fondaparinux. Protamine sulfate has no effect on the anticoagulant activity of fondaparinux because it fails to bind to the drug. Recombinant activated factor VII reverses the anticoagulant effects of fondaparinux in volunteers, but it is unknown whether this agent controls fondaparinux-induced bleeding.

Parenteral Direct Thrombin Inhibitors Direct thrombin inhibitors bind directly to thrombin and block its interaction with its substrates. Approved parenteral direct thrombin inhibitors include recombinant hirudins (lepirudin and desirudin), argatroban, and bivalirudin (Table 143-7). Lepirudin and argatroban are licensed for treatment of patients with HIT, desirudin is licensed for thromboprophylaxis after elective hip arthroplasty, and bivalirudin is approved as an alternative to heparin in patients undergoing percutaneous coronary intervention, including those with HIT.

LEPIRUDIN AND DESIRUDIN Recombinant forms of hirudin, lepirudin, and desirudin are bivalent direct thrombin inhibitors that interact with the active site and exosite 1, the substrate-binding site on thrombin. For rapid anticoagulation, lepirudin is given by continuous IV infusion, but the drug can be given SC. Lepirudin has a plasma half-life of 60 min after IV infusion and is cleared by the kidneys. Consequently,

TABLE 143-7 COMPARISON OF THE PROPERTIES OF LEPIRUDIN, BIVALIRUDIN, AND ARGATROBAN

	Lepirudin/ Desirudin	Bivalirudin	Argatroban
Molecular mass	7000	1980	527
Site(s) of interaction with thrombin	Active site and exosite 1	Active site and exosite 1	Active site
Renal clearance	Yes	No	No
Hepatic metabolism	No	No	Yes
Plasma half-life (min)	60 (IV) 120–180 (SC)	25	45