CHAPTER 145
Antithrombotic and Thrombolytic Therapy
GOHAR H. DAR and STEVEN R. INSLER

INTRODUCTION
The occurrence of venous and arterial thromboembolism has had a large impact on medical care and is a major cause of both morbidity and mortality. Arterial thromboembolism, commonly implicated in myocardial infarctions (MIs), stroke, and limb ischemia, is responsible for more deaths each year than the next seven leading causes of death combined (1,2). Venous thrombosis may lead to pulmonary embolism, right heart dysfunction, venous insufficiency, and postthrombotic syndrome (3). The incidence of patients in the intensive care unit developing venous thromboembolism ranges from 5% to 33% (4–6). There are an estimated 2 million cases of venous thromboembolism each year in the United States alone, with an annual estimated mortality of about 60,000 from pulmonary embolism (7–9). The ability to rapidly diagnose and initiate effective therapy is paramount. This chapter will briefly review the formation of arterial and venous thrombi, regulation of the coagulation cascade, and current antithrombotic and thrombolytic therapies.

THROMBogensIs And COAGulation
Deep venous thromboemboli are associated with many different clinical situations, and the stimulus for developing thrombi depends on the underlying clinical condition. A patient may have an underlying primary hypercoagulable predisposition to developing venous thrombosis secondary to decreased antithrombotic or increased prothrombotic proteins (thrombophilias) (10), increasing the relative risk of thrombosis up to 10-fold. Deep venous thrombosis (DVT) will form under conditions of low flow and are predominantly composed of fibrin and red blood cells. They usually originate in the muscular calf veins or in the valve cusps of the deep calf veins (1). The risk factors for DVT are listed in Table 145.1.

In vivo, coagulation in the veins is initiated by a complex of tissue factor (TF), a type I transmembrane protein—and the serine protease factor VIIa. Low levels of factor VIIa circulate in plasma so that the system will respond efficiently if vessel injury occurs and TF is exposed; the factor VIIa/TF complex activates factors IX and X. Activated factor X cleaves small amounts of prothrombin to generate thrombin. The low concentrations of thrombin generated are sufficient to activate factors V and VIII, essential steps for the propagation of the coagulation cascade (Fig. 145.1) (11–13).

Arterial thrombi typically form under high flow (shear) conditions, and are made up primarily of platelet aggregates held together by fibrin strands. Most arterial thrombi are superimposed on ruptured atherosclerotic plaques. Arterial plaque rupture exposes thrombogenic material in the lipid-rich core of the blood (14). When plaques rupture, subendothelial collagen and von Willebrand factor are exposed; collagen and von Willebrand factor provide a substrate for platelet adhesion (15,16). Collagen binds to platelets’ glycoprotein Ia/IIa receptor complex; von Willebrand factor binds to glycoprotein Ib/IX/V receptor complex; and other exposed extracellular matrix, such as fibronectin and laminin bind to glycoprotein VI. These actions cause the up-regulation of platelet glycoprotein IIb/IIIa receptor complex, which in turn results in platelet aggregation. Glycoprotein IIb/IIIa accelerates platelet adhesion to the subendothelium by binding to fibrinogen and von Willebrand factor (17,18). Additionally, plaque rupture causes TF release, which accelerates the extrinsic coagulation cascade (Fig. 145.2).

Once coagulation is initiated in either veins or arteries, and TF has activated factor VII, converting it to factor VIIa, the factor VIIa/TF complex activates factors IXa and Xa, respectively. Factor IXa binds to factor VIIIa on the membrane surfaces to form intrinsic tenase, which activates factor X; by feedback activation of factor VII, factor Xa initiates and amplifies coagulation (19,20).

Factor Xa propagates coagulation by binding with factor Va, and in turn activates prothrombin to thrombin and, ultimately, to fibrin clot formation. If the thrombus is of sufficient size to disrupt blood flow, shear increases and promotes additional platelet and fibrin deposition.

Regulation of the Coagulation Cascade
Three inhibitory systems are involved in the regulation of the coagulation cascade. The pathway of TF inhibition interferes with the initiation of coagulation. The protein C pathway regulates thrombin generation and inhibits the propagation of coagulation. Antithrombin blocks the generation of thrombin and, subsequently, thrombin activity. Additionally, the fibrinolytic system promotes fibrin degradation.

Tissue Factor Pathway Inhibitor
The factor VIIa/TF complex is inhibited by the TF pathway inhibitor, most of which is bound to endothelium, in two steps. First, the TF pathway inhibitor binds and then inactivates factor Xa. This complex in turn inactivates factor VIIa, which is bound to TF (12).

Protein C Pathway
The protein C pathway is initiated when thrombin binds to thrombomodulin, which is found on endothelium. Once bound to thrombomodulin, thrombin undergoes a conformational change at its active site, which converts it from a procoagulant enzyme to a potent activator of protein C. Activated protein C, a vitamin K–dependent protein, acts as an anticoagulant by proteolytically degrading and inactivating factors Va and VIIIa, thus blocking thrombin generation (21).
Antithrombin

Antithrombin inhibits thrombin, factor Xa, and other activated clotting factors, but in the absence of heparin, these reactions occur slowly. Heparin addition will increase the rate of inhibition of these reactions by 1,000-fold (22). Small amounts of the proteoglycan heparan sulfate located on the luminal surface may maintain intact endothelium in a non-thrombogenic state (23).

Fibrinolytic Degradation of Fibrin

This system is designed to remove intravascular fibrin and restore normal blood circulation. Fibrinolysis is initiated by plasminogen activators that convert plasminogen to plasmin, a trypsinlike protease. Plasmin degrades fibrin into soluble fibrin degradation products (24).

D-Dimers. D-Dimers are a specific fibrin degradation product formed only by plasmin degradation of fibrin and not by plasmin degradation of intact fibrinogen (Fig. 145.3). Thus, its presence indicates that fibrin has been formed. d-Dimer has been validated as a diagnostic tool to help in the exclusion of venous thrombosis and pulmonary embolism and is widely used in the emergency room setting for this purpose (25–27). Elevated d-dimer levels have been reported as a marker of risk for both multiple organ failure and death in critically ill patients (28).

Antiplatelet Agents

Platelet aggregation leading to a disruption of blood flow can have devastating outcomes, often causing permanent disability or death. The understanding of normal platelet function has led to the rational basis for the development of antiplatelet agents.

Aspirin

The efficacy of aspirin in acute coronary syndrome (ACS) has been established in numerous clinical trials. For example, the International Study of Infarct Survival (ISIS)-2 demonstrated that for acute MI, aspirin alone reduced mortality to a similar extent as did streptokinase alone, with an additive benefit when both agents were used (29). A recent meta-analysis by the Antiplatelet Trialists’ Collaboration found that aspirin reduced the risk of MI, stroke, or death from 13.3% to 8.0% in patients with unstable angina (30). The meta-analysis also found that the greatest risk reduction occurred with a dose of 75 to 150 mg per day; higher doses such as 325 mg per day did not appear to confer any added benefit. In a subsequent investigation, the CURRENT/OASIS-7 (Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs—Organization to Assess Strategies in Ischemic Syndromes) trial compared the effectiveness of double-dose clopidogrel versus a standard dose for 30 days.

<table>
<thead>
<tr>
<th>TABLE 145.1 Potential Mechanisms by which Various Clinical Conditions May Facilitate Deep Venous Thrombosis (DVT)</th>
</tr>
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<tbody>
<tr>
<td><strong>Increased Baseline Propensity for Thrombosis</strong></td>
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<tr>
<td>Hypercoagulability</td>
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<td><strong>Direct vessel injury</strong></td>
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<td><strong>Blood stasis</strong></td>
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AT, antithrombin; HRT, hormone replacement therapy; OCT, oral contraceptives; ?, may or may not be effective.

Risk factors or clinical conditions that increase the risk of DVT can be classified as either increasing the baseline propensity for thrombosis or precipitating the thrombotic event acutely. Thrombosis may occur by one of three major mechanisms: inducing hypercoagulability, directly injuring the vessel wall, or causing blood stasis (low flow).

coupled to an open label randomization to high (300 to 325 mg/day) versus a low dose (75 to 100 mg/day) of aspirin in 25,086 patients with ACSs undergoing invasive therapy. This study found no significant difference between either regimen with respect to the primary outcome of cardiovascular death, infarction, or stroke. It did however note a small increase in the incidence of major gastrointestinal bleeding among patients receiving the higher-dose aspirin regimen as compared to the lower dosage (47 patients [0.4%] vs. 29 patients [0.2%]; p = 0.04) (31). Aspirin therapy has, thus, become the standard for the secondary prevention of cardiovascular events in high-risk patients. The role of aspirin alone, versus other antithrombotic agents, in atrial fibrillation has been addressed in many studies, the results suggesting that the risk reduction of ischemic strokes associated with oral vitamin K–inhibiting anticoagulant therapy is greater than that provided by aspirin (32,33).

**Aspirin Resistance**

The efficacy of aspirin in the inhibition of platelet function differs between patients. Cardiovascular events occur preferentially in patients with low responses to aspirin therapy (34), referred to as aspirin resistance. The prevalence is reported to vary between 5% and 60%, depending on the laboratory studies used (35). Gum et al. (36), in a prospective study, followed 325 patients with stable coronary artery disease for 2 years, finding aspirin resistance in 5.5% of patients using optical platelet aggregability, and in 9.5% by using the Platelet Function Analyzer 100 (PFA-100). Aspirin-resistant patients were noted to have a 24% risk of death, MI, or stroke, as compared with a 10% risk for patients who were aspirin sensitive.

There are two aspects of resistance: biochemical and clinical. Biochemical resistance refers to the inability of aspirin to initiate platelet inhibition, whereas clinical resistance indicates an increased risk of cardiovascular events in patients receiving treatment with aspirin (37). Platelet receptor polymorphism is thought to be responsible for aspirin resistance (38).

The risk of hemorrhage, especially from the gastrointestinal tract, is a major concern when doses higher than 325 mg per day are used. The local effect of aspirin on the gastric mucosa is more prevalent with the higher doses, but patients with vascular malformations or mucosal lesions may bleed at lower doses. There is also a risk of cerebral hemorrhage in patients with prior stroke or with uncontrolled hypertension. In the event of hemorrhage, aspirin should be discontinued and the patient observed but, if needed, the patient may be

**Figure 145.1** Model for venous thrombosis. Coagulation in veins is initiated by the tissue factor-VIIa complex which then activates factors IX and X. Factor II, prothrombin; factor IIa, thrombin; PSGL-1, p-selectin glycoprotein ligand-1.
treated with fresh platelet transfusion. For elective surgical procedures, aspirin should be stopped 5 days before the intervention (39). Aspirin is not recommended for venous thromboembolic prophylaxis (40); other forms of standard venous thromboembolism prophylaxis—for example, subcutaneous heparin and pneumatic compression devices—are preferred.

**P2Y12 Receptor Antagonists**

Adenosine diphosphate (ADP) interacts with two different receptors on platelets, known as P2Y1 and P2Y12. Interaction with P2Y1 receptors initiates the platelet response while interaction with P2Y12 receptors promotes the response. Blockade of the effects of ADP at either of these receptors results in a marked reduction in the overall effect of ADP on platelet function. The initial response to ADP is a change in the shape of the platelet; the disc-shaped cells will convert into a spherical form from which pseudopodia emerge. This change, mediated by the P2Y1 receptor, involves Ca²⁺ influx, intracellular Ca²⁺ mobilization, and actin polymerization. Interaction of ADP with the P2Y12 receptor results in inhibition of adenylate cyclase, which is accompanied by platelet aggregation (41,42). P2Y12 inhibition is recommended for patients undergoing antiplatelet therapy for the prevention of ischemic events.

The thienopyridine (ticlopidine, clopidogrel, and prasugrel) and nonthienopyridine (cangrelor and ticagrelor) class of antiplatelet agents have been approved for clinical use. These medications achieve their antiplatelet effect by irreversibly blocking the binding of ADP to the specific platelet receptor P2Y12, thus inhibiting adenyl cyclase and platelet aggregation (Fig. 145.4).

**Clopidogrel**

Clopidogrel, a member of the thienopyridine family, is a potent platelet inhibitor, working by irreversibly binding to low-affinity ADP receptors. It is rapidly absorbed and metabolized by the hepatic cytochrome P450 enzyme system to an active metabolite that selectively and irreversibly inhibits ADP-induced platelet aggregation. This metabolite also impairs the activation of glycoprotein (GP) IIb/IIIa complex and prevents fibrinogen binding to the platelets. Platelets exposed to this drug are affected for the remainder of their life span. Dose-dependent platelet inhibition can be seen within 2 hours after a single oral dose. For maximum effect, patients may be given a loading dose of 300 to 600 mg, followed by 75 mg per day. With repeated doses of 75 mg per day, maximum platelet inhibition can be achieved within 3 to 7 days (43).

When steady state is achieved, platelet aggregation is inhibited by 40% to 60% (44). Prolongation of bleeding time...
is independent of age, renal impairment, or gender. Platelet aggregation and bleeding time generally return to baseline about 5 days after discontinuation of clopidogrel. The CAPRIE trial was among the first to establish that clopidogrel is more effective than aspirin in reducing atherosclerotic events—including peripheral vascular disease, MI, and stroke—by 8.7% (45). The efficacy and safety of clopidogrel have been evaluated in ACS patients in the CURE trial, showing a 20% relative risk reduction in composite triple end points: nonfatal MI, death, or stroke (46). Clopidogrel, like ticlopidine, prolongs the bleeding time. While there was an incidence of neutropenia reported at 0.1% in the CAPRIE trial, there have been rare case reports of clopidogrel-associated thrombotic thrombocytopenic purpura. The incidence of gastrointestinal bleeding is less when compared to aspirin, but the incidence of bleeding is higher among patients requiring urgent surgical procedures who take clopidogrel (47). However, the clopidogrel effect can be reversed by transfusion of fresh platelets.

**Ticlopidine**

Ticlopidine, an older thienopyridine compound, inhibits platelet aggregation irreversibly and interferes with ADP-induced binding of fibrinogen to platelet receptors. It has fallen out of favor because of two major side effects: neutropenia and thrombotic thrombocytopenic purpura. Rare case reports of severe bone marrow toxicity limit ticlopidine use to patients who are intolerant or unresponsive to aspirin.

**Prasugrel**

Prasugrel, a third-generation thienopyridine, is an orally administered irreversible platelet P2Y12 receptor antagonist. It is a prodrug and requires metabolism via a cytochrome P450–dependent pathway into its active metabolite. Compared to clopidogrel, it has a more rapid onset of action after oral administration, it achieves and renders a more consistent and predictable platelet inhibition in individual patients (48).
This occurs because the metabolism of prasugrel is different than clopidogrel and there are greater and more predictable amounts of active metabolite produced. This leads to longer recovery of platelet function (7 days for a 75% return to baseline platelet function as opposed to 5 days for clopidogrel). Surgical bleeding may be more problematic as a result (49).

In patients with ACSs undergoing percutaneous coronary intervention (PCI), prasugrel offers more effective antithrombotic therapy when compared to clopidogrel as shown in the TRITON-TIMI 38 study (trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in MI 38) (48). This was a double-blinded, randomized controlled trial directly comparing prasugrel (60-mg loading dose followed by a 10-mg maintenance dose) and standard clopidogrel (300-mg loading dose followed by a 75-mg maintenance dose). The primary efficacy end point (cardiovascular death, nonfatal MI, or nonfatal stroke) occurred significantly less often in patients treated with prasugrel (9.9 vs. 12.1%; \( p < 0.001 \)). The rate of probable stent thrombosis was significantly decreased in the prasugrel group (1.1 vs. 2.4%; \( p < 0.001 \)). There was, however, a significant increase in bleeding associated with prasugrel in comparison to clopidogrel (2.4 vs. 1.8%; \( p = 0.03 \)), most notable in patients with a prior history of stroke, age >75 years, and those with a body weight of <60 kg. Prasugrel effects are not modulated by aspirin dose or cytochrome interfering drugs including proton pump inhibitors. A washout period of 7 days is indicated for prasugrel-treated patients requiring surgery.

**Ticagrelor**

Ticagrelor is an orally administered cyclopentyltriazolopyrimidine, a new compound class very different from both clopidogrel and prasugrel, ticagrelor interacts with P2Y12 receptors on platelets, disabling their ability to interact with ADP. Although this compound is metabolized to an active agent, it is chemically very similar to the parent compound and metabolic conversion is not required for receptor interaction. It directly binds to the platelet receptor and allows for a faster onset of action, more intense, and consistent platelet inhibition than does clopidogrel (50). The reversible binding effects and the plasma half-life of 8 to 12 hours necessitate twice daily dosing (51). The ONSET/OFFSET study demonstrated ticagrelor exhibited greater platelet inhibition than clopidogrel. It looked at 123 patients with stable coronary artery disease on aspirin therapy and compared the addition of clopidogrel (600 mg load followed by 75 mg/day maintenance) or ticagrelor (180 mg load followed by 90 mg twice daily) or placebo. Analysis performed 2 hours after the loading doses demonstrated 90% of patients receiving ticagrelor achieved greater than 70% platelet inhibition compared to clopidogrel. This effect was sustained at 6 weeks with patients taking ticagrelor (51).

Additionally, the PLATO trial (Platelet Inhibition and Patient Outcomes) examined the clinical benefit of ticagrelor (180-mg loading dose followed by 90 mg twice daily) compared to clopidogrel (300- to 600-mg loading dose followed
by 75 mg daily) in 18,624 patients with ACSs randomized to receive either medication as soon as possible after hospital admission. The PLATO trial demonstrated that ticagrelor significantly reduced the rate of the primary end point (death from vascular causes, nonfatal myocardial infarct, or nonfatal stroke) at 12 months (9.8% vs. 11.7%; Hazard Ratio 0.84, p = 0.0001). There were no significant differences in the rate of major bleeding between either medication (11.6% vs. 11.2%, respectively), but ticagrelor was associated with a significantly higher rate of major bleeding not related to coronary artery bypass grafting (4.5% vs. 3.8%) (52).

Ticagrelor has been approved for clinical use and is indicated for the prevention of atherothrombotic events in patients with ACSs, including patients managed medically and invasively. In addition to being contraindicated in patients at high risk for bleeding, ticagrelor is contraindicated in patients with prior hemorrhagic stroke and severe hepatic dysfunction (50).

Cangrelor
Cangrelor is an intravenous, rapid onset, potent, and direct-acting platelet ADP P2Y12 inhibitor that has rapidly reversible effects. When a bolus of cangrelor is administered, the antiplatelet effect is immediate, and the effect can be maintained with a continuous infusion. The plasma half-life of cangrelor is approximately 3 to 5 minutes, and platelet function is restored within 1 hour after cessation of the infusion (53).

In the CHAMPION PHOENIX trial, 11,145 patients undergoing either urgent or elective percutaneous coronary intervention (PCI) were enrolled in a double-blind, placebo controlled manner to evaluate the impact of clopidogrel and cangrelor on outcome; patients received guideline-recommended therapy of a bolus and infusion of cangrelor or a loading dose of 600 mg or 300 mg of clopidogrel. The primary efficacy end point was a composite of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours after randomization; the key secondary end point was stent thrombosis at 48 hours. The rate of the primary efficacy end point was 4.7% in the cangrelor group and 5.9% in the clopidogrel group (adjusted odds ratio with cangrelor, 0.78; 95% confidence interval [CI], 0.66 to 0.93; p = 0.005). The rate of the primary safety end point was 0.16% in the cangrelor group and 0.11% in the clopidogrel group (odds ratio, 1.50; 95% CI, 0.53 to 4.22; p = 0.44). Stent thrombosis developed in 0.8% of the patients in the cangrelor group and in 1.4% in the clopidogrel group (odds ratio, 0.62; 95% CI, 0.43 to 0.90; p = 0.01). The rates of adverse events related to the study treatment were low in both groups; the primary safety end point was severe bleeding at 48 hours (54). At the time of this writing, the U.S. Food and Drug Administration (FDA) is continuing to evaluate cangrelor for approval.

Vorapaxar
In 2014, the FDA approved a new class of antiplatelet medication, to reduce the risk of MI or peripheral artery disease (PAD). This class of medication, considered a protease–activated-receptor 1 antagonist (PAR-1), is intended as part of a therapeutic regimen inclusive of aspirin and clopidogrel.

Approval of this medication was based on the Thrombin-Receptor Antagonist in Secondary Prevention of Atherosclerotic Ischemic Events (TRA 2 P TIMI-50) trial. Results of the trial (n = 26,499 patients) demonstrated cardiovascular death, MI, stroke, or urgent coronary revascularization was decreased by 13% in patients taking vorapaxar. When coronary revascularization was excluded, the secondary endpoint of cardiovascular death, MI, or stroke was also significantly reduced (55). Because of vorapaxar’s antiplatelet effects, moderate or severe bleeding occurred in 3.4% of patients compared with 2.1% in the placebo-treated patients. Intracranial hemorrhage occurred in 0.6% of those taking vorapaxar compared with 0.4% taking placebo (55).

**Glycoprotein IIb/IIIa Antagonists**

**Abciximab**
This, the most successful GPIIb/IIIa antagonist, is a human-murine Fab chimeric monoclonal antibody fragment to the GPIIb/IIIa binding site; it is a large protein with a rapid and prolonged response, causing the bleeding time to remain elevated for 12 hours after injection. Abciximab is used in combination with aspirin and heparin in patients with unresponsive unstable angina or undergoing PCI. It has been demonstrated to deliver a 60% relative risk reduction in triple end points: MI, emergent revascularization, or cardiovascular deaths (56,57). The major complications of this agent include intracranial bleeding or a decrease in hemoglobin of more than 15%, reported as frequently as 10.5% (58). There is a high incidence of thrombocytopenia, which can be spurious (4%) due to platelet clumping, but true and severe thrombocytopenia may also develop, resulting in profound bleeding (59). In the event of profuse bleeding, platelet transfusions are required to normalize the platelet count. Desmopressin has been shown to normalize the bleeding time (60).

**Eptifibatide**
This disintegrin, derived from the southeastern pygmy rattle-snake, is rapidly bound and rapidly reversed, with a normalization of the bleeding time within 1 to 4 hours. This drug has been shown to be more effective in milder forms of ACSs (61).

**Tirofiban**
This is a small nonpeptide compound derived from tyrosine, which interacts with the arginine-glycine-aspartic acid fibrinogen receptor. Tirofiban has been used in unstable angina with mixed results (62).

**Dipyridamole**
Dipyridamole is a phosphodiesterase inhibitor, reversibly inhibiting platelet aggregation. As it increases c-AMP and c-GMP levels, through its inhibition of phosphodiesterases, it potentiates the effect of nitric oxide. It has been used adjunctively with aspirin to reduce stroke events in patients younger than 70 years (63).

**ANTITHROMBOTIC THERAPY**

**Unfractionated Heparin**
Unfractionated heparin (UF) is a naturally occurring acidic glycosaminoglycan. Its pentasaccharide sequence binds to antithrombin, causing a conformational change at the arginine reactive site that potentiates the effect of antithrombin,
causing it to have an enhanced effect on inhibition of the coagulation enzymes, in particular thrombin (factor IIa) and factor Xa. Heparin also acts to inhibit activation of factors V and VIII by thrombin (Fig. 145.5) (64,65). The increase in inhibition of these enzymes in the presence of UH may be up to 2,000 times faster than in its absence. The molecular weight of UH is 3,000 to 35,000 daltons (d) on average, with a mean molecular weight of 15,000 d, composed of approximately 45 monosaccharide chains. Due to the variable size and structure of heparin, only about one-third of any given dose of heparin will demonstrate therapeutic anticoagulant activity. The different-sized molecules are cleared at different rates by the kidney, with the larger ones being cleared more rapidly. Thus, the combination of these factors leads to great variability in the anticoagulant effects on individuals, necessitating the need for monitoring with activated partial thromboplastin time (aPTT). Heparin is obtained from either bovine lung or porcine intestine and is available as a sodium or calcium salt.

**Uses of Unfractionated Heparin**

Heparin is indicated for prophylaxis of venous thromboembolism. It is used in the treatment of DVT and pulmonary embolus, as well as for early treatment of patients suffering from ACSs.

**Prevention of Thromboembolism.** To prevent thromboembolism, UH at a fixed low dose of 5,000 units, subcutaneously every 8 to 12 hours, results in a 60% to 70% relative risk reduction for DVT and fatal pulmonary embolus (PE) (40,67). In high-risk surgical and acutely ill medical patients, the use of low–molecular-weight heparin (LMWH) is becoming the standard for prevention of thrombosis (68,69).

In the patient who is unable to tolerate any type of anticoagulation, the use of intermittent pneumatic compression is useful as a mechanical means for preventing DVT by intermittently squeezing the patient’s calves, leading to increased blood flow through the venous system. Intermittent pneumatic compression may also stimulate fibrinolysis by stimulating the vascular endothelium (70).

**Venous Thromboembolism and Pulmonary Embolus.** Therapy for treating proximal or symptomatic distal venous thromboembolism and PE is aimed at preventing extension.
of the clot with further embolization and recurrence; anticoagu-
alization has long been an effective strategy for the treatment of both conditions (71). Multiple studies have demonstrated the efficacy of heparin in reducing mortality in patients with venous thromboembolism (72,73), as well as the high mortality in patients with PE who are not anticoagulated (74). More recent clinical studies further demonstrated the benefit of treating DVT with continuous intravenous heparin and, in some cases, LMWH (75–77). Additionally, data show the effectiv-
ess of using subcutaneous heparin as the initial treatment for DVT, as long as adequate doses are used and the aPTT is pro-
longed into the therapeutic range (78–80). Recently, Kearon et al. (81) demonstrated that administration of a fixed dose, weight-adjusted, UH was as effective and safe as the admin-
istration of LMWH in patients with acute DVT and may also be suitable for treatment in the outpatient setting.

Perhaps the most efficient method for initiating intrave-
nous heparin therapy is using weight-adjusted nomograms. The important consideration is to maintain a therapeutic range when heparin anticoagulation therapy is initiated, best achieved with frequent monitoring of plasma aPTT. Subthera-
pic dosing within the first 24 hours of a documented DVT resulted in a significantly greater frequency of venous thromboembolus recurrence when compared to those patients who reached a supratherapeutic threshold within 24 hours (82).

The weight-based method was developed by Raschke et al. (83) who found that a weight-based titration of UH resulted in a significant decrease in the time required to reach therapeutic levels as compared to a standard dosing scheme of heparin. These clinicians found that 97% of patients dosed using the weight-based nomogram achieve therapeutic levels within 24 hours of initiation as opposed to 77% in the standard dos-
ing group (Tables 145.2 and 145.3).

Typically, the Raschke method of anticoagulation in the acute phase of venous thromboembolism is initiated with an intravenous loading dose of 80 units/kg, followed by 18 units/kg/hr. Subsequent doses should be adjusted using a standard nomogram to rapidly reach and maintain an aPTT that corresponds to therapeutic heparin levels of 1.5 to 2.5 times the baseline (83–88). Alternatively, therapeutic heparin anti-
coagulation is determined by achieving a plasma anti-factor Xa level of 0.35 to 0.7 units/ml (89,90). This therapeutic range is recommended based on animal studies (91), prospective studies and analysis of patients with established DVT (90), studies on the prevention of mural thrombus formation following MI (91) and prevention of recurrent ischemia following coro-
mary thrombolysis (93). Heparin anticoagulation should be continued for up to 5 days so that adequate anticoagulation is achieved. During this time, the aPTT should be monitored every 6 hours until the therapeutic range is achieved, and once daily thereafter. Preferably on day 1, the patient may be tran-
sitioned to long-term warfarin (5 mg), a vitamin K–antagonist agent that may be administered orally if the patient can tolerate enteral intake. The anticoagulation effect of warfarin is moni-
tored by the international normalized ratio (INR) to achieve a therapeutic range of two to three times the normal level for a first thrombotic episode. Warfarin is considered to be at therapeu-
tic level if the INR of 2 to 3 is maintained for 2 consecutive days. If the patient is unstable and unable to tolerate oral anti-
coagulation, intravenous heparin may need to be continued. It is important to keep in mind that warfarin interacts with many commonly used drugs in the ICU, and its metabolism may be affected by hepatic and renal impairment. This may lead to erratic variation in the anticoagulant effect of warfarin, exposing the patient to increased risks of bleeding and throm-
botic complications (7). The minimum recommended duration of warfarin therapy is 3 months (66,94) based upon the clinical scenario and patient risk factors, with follow-up evaluation to determine if longer therapy is necessary. Further studies have demonstrated that longer treatment may be beneficial (95–97) in higher-risk patients. In accordance with the American Col-
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### Table 145.2 Weight-Based Heparin Dosing Nomogram

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<tr>
<th>aPTT&lt;sub&gt;c&lt;/sub&gt;, s&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Dose Change (U/kg/hr)</th>
<th>Additional Action</th>
<th>Next aPTT (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35 (&lt;1.2× mean normal)</td>
<td>+4</td>
<td>Rebolus with 80 IU/kg</td>
<td>6</td>
</tr>
<tr>
<td>35–45 (1.2–1.5× mean normal)</td>
<td>+2</td>
<td>Rebolus with 40 IU/kg</td>
<td>6</td>
</tr>
<tr>
<td>46–70 (1.5–2.3× mean normal)</td>
<td>0</td>
<td>0</td>
<td>6&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>71–90 (2.3–3.0× mean normal)</td>
<td>–2</td>
<td>Stop infusion</td>
<td>6</td>
</tr>
<tr>
<td>&gt;90 (&gt;× mean normal)</td>
<td>–3</td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

<sup>a</sup> aPTT, activated prothrombin time.

<sup>b</sup> Therapeutic range in seconds should correspond to a plasma heparin level of 0.2–0.4 U/ml by protamine sulfate or 0.3–0.6 U/ml by amidolytic assay. When aPTT is checked at 6 hrs or longer, steady-state kinetics can be assumed.

<sup>c</sup> Heparin, 25,000 IU in 250 mL D,W, Infuse at rate dictated by body weight.

<sup>d</sup> During the first 24 hrs, repeat aPTT every 6 hrs. Thereafter, monitor aPTT once every 8 hrs unless it is outside the therapeutic range.


### Table 145.3 Guidelines for Anticoagulation Using Unfractionated Heparin

<table>
<thead>
<tr>
<th>VTE suspected</th>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain baseline aPTT, PT, CBC</td>
<td></td>
</tr>
<tr>
<td>Check for contraindication to heparin therapy</td>
<td></td>
</tr>
<tr>
<td>Order imaging study, consider giving heparin 5,000 IU IV</td>
<td></td>
</tr>
<tr>
<td>VTE confirmed</td>
<td></td>
</tr>
<tr>
<td>Rebolus with heparin 80 IU/kg IV and start maintenance infusion at 18 IU/kg (see Table 145.2)</td>
<td></td>
</tr>
<tr>
<td>Check aPTT at 6 hrs to keep aPTT in a range that corresponds to a therapeutic blood heparin level (see text and Table 145.2)</td>
<td></td>
</tr>
<tr>
<td>Check a platelet count between days 3 and 5</td>
<td></td>
</tr>
<tr>
<td>Start warfarin therapy on day 1 at 5 mg and adjust subsequent daily dose according to INR</td>
<td></td>
</tr>
<tr>
<td>Stop heparin therapy after at least 3–5 of combined therapy when INR is 2.0</td>
<td></td>
</tr>
</tbody>
</table>
| Anticoagulate with warfarin for at least 3 mo at an INR of 2.5; range: 2.0–3.0 | (see Table 145.6)
Thrombolytic Therapy, it is now recommended that warfarin therapy be continued following a first unprovoked proximal or second unprovoked DVT or those with active cancer. For those with recurrent events or who have permanent or long-term risk factors, the panel recommends indefinite therapy (94).

**Acute Coronary Syndromes.** The ACC/AHA updated guidelines for the management of patients with acute myocardial infarction (AMI) (98) evaluated multiple trials comparing the use of LMWH with UH in non–ST elevation ACS (99–101). The studies cited demonstrate, as a whole, a benefit of LMWH over UH when it came to a lower event rate and relative risk reduction (102). These guidelines suggest considering LMWH, as opposed to UH due to its greater inhibition of factor Xa, the ability to administer the drug subcutaneously, and its high bioavailability. In those patients with impaired renal function (CrCl <30 mL/min) it may be necessary to consider a reduction in dose to one-half recommended and/or frequency of administration to only once daily. It should be noted that a sub study of the Enoxaparin and Thrombolysis Reperfusion for AMI-TIMI 25 trial demonstrated that for every 30 mL/min decrease in CrCl, the risk of major and minor bleeding increased by 50% (103,104). Until conclusive results are available regarding optimal dosing, it may be safer to use UH in patients with impaired renal function presenting with ACS. However, other benefits of the drug are cited as well, such as the potential to prevent thrombin generation and inhibit thrombin, the lack of need to monitor coagulation, and the lower incidence of heparin-associated thrombocytopenia (105).

**Monitoring UH**

The most widely used test for evaluating the adequacy of heparin anticoagulation is the aPTT, a global coagulation test that is not always a reliable indicator of plasma heparin levels and/or the antithrombotic activity of heparin. The aPTT can be impacted by various acute phase reactant plasma proteins, including factor VIII. Additionally, the aPTT can be influenced by the coagulation timer and reagents used to perform the test (103). If a hospital is unable to measure plasma heparin levels directly, it is recommended that each laboratory standardize the therapeutic range of the aPTT to correspond to plasma levels of 0.3 to 0.7 IU/mL anti–factor Xa activity by an amidolytic assay.

**Complications of Anticoagulation Therapy**

**Heparin Resistance**

Patients are considered heparin resistant if their daily requirement of heparin exceeds 35,000 units/24 hr; unfortunately, multiple studies demonstrate that at least 25% of patients with venous thromboemboli are heparin resistant. Heparin resistance may be associated with antithrombin deficiency, increased heparin clearance, increases in heparin-binding proteins, and increases in factor VIII, fibrinogen, and platelet factor 4. Aprotinin and nitroglycerin have been reported to cause drug-induced resistance, but the association with nitroglycerin remains controversial (106). Factor VIII and fibrinogen are elevated in response to acute illness or pregnancy. Elevation of factor VIII alters the response of the aPTT to heparin without decreasing the antithrombotic effect, as the anticoagulant effect measured by the plasma aPTT and the antithrombotic effect is measured by anti–factor Xa activity become dissociated.

For those patients considered heparin resistant, the dose of heparin should be adjusted to maintain the anti–factor Xa heparin levels between 0.35 and 0.7 mIU/mL. In a randomized, controlled study by Levine and Hirsch (107), evaluating 131 patients with venous thromboembolism and manifesting heparin resistance, monitoring the aPTT was compared to anti–factor Xa activity; while there were no difference in clinical outcomes, it was found that the patient group monitored with anti–factor Xa heparin levels required significantly less heparin with no differences in bleeding.

**Hemorrhagic Complications**

The incidence of major hemorrhagic complications—defined as intracranial or retroperitoneal hemorrhage, hemorrhage requiring a transfusion, or hemorrhage directly related to death—from therapeutic anticoagulation is less than 5% (105). The risk increases with age, total dose of heparin/24 hr. patient premorbid condition, concomitant use of aspirin, GPIIb/IIIa antagonists, or thrombolytic therapy. Intravenous (IV) heparin infusion appears to produce less marked bleeding complications than when the agent is administered (107) subcutaneously. This may be due to a lower total dose of heparin via the IV, as compared to the subcutaneous, route (106).

The anticoagulant effect of UH can be neutralized rapidly by intravenous protamine. Protamine is a cationic protein derived from fish sperm that strongly binds to the anionic heparin compound in a ratio of approximately 100 units of UH/mg of protamine. When heparin has been infused, only the heparin given over the prior 2 hours should be included in the calculation. If the heparin infusion was discontinued for more than 30 minutes but less than 2 hours, use one-half of the calculated protamine dose. If the infusion was discontinued for longer than 2 hours, use one-quarter of the calculated protamine dose. One should avoid giving 50 mg of protamine at one time and, if given by infusion, it should not exceed 5 mg per minute to reduce the incidence of adverse reactions. Heparin neutralization can be confirmed by a fall in the aPTT.

The risks of severe adverse reactions to protamine, such as hypotension and bradycardia, are reduced with a slow administration of the drug over more than 3 minutes. Some clinicians will begin the protamine infusion following a 3- to 5-mg test dose administered over 1 minute (107,108). Allergic reactions including anaphylaxis are associated with a previous exposure to protamine-containing insulin—for example, NPH-insulin (108)—fish hypersensitivity (109), and vasectomy. Patients at risk for developing antiprotamine antibodies can be pretreated with corticosteroid and antihistamine medications.

**Heparin-Associated (Induced) Thrombocytopenia**

Heparin-induced thrombocytopenia (HIT) is an antibody-mediated adverse reaction to the administration of heparin and/or LMWH and may lead to both arterial and venous thrombosis. The diagnosis is made both on clinical and serologic findings. HIT antibody formation, accompanied by an otherwise unexplained fall in platelet count by more than 50% from baseline and/or skin lesions at injection sites are the manifestations of HIT (110).

The incidence of HIT is less than 1% when heparin is given for less than 7 days; thereafter, when given to patients with an extended need for anticoagulation (such as ICU patients),
Once the determination of HIT is made, it is not adequate simply to stop anticoagulation therapy with heparin or LMWH. Multiple studies document that patients continue to be at risk of thrombosis if no anticoagulation is given (112,113). Currently, alternative antithrombotic agents are being used and have been approved in many countries for the treatment of HIT. Three of the agents are direct thrombin inhibitors: argatroban, hirudin (lepirudin), and bivalirudin, and the other agent is a heparinoid, danaparoid (Table 145.4).

Argatroban is a small (MW 526) synthetic molecule derived from L-arginine that reversibly binds to thrombin. It is approved for prophylaxis and treatment of patients with HIT in both the United States and Canada. It reportedly has been associated with a lower thrombotic event rate in one prospective study. The half-life is less than 1 hour, and the drug is excreted normally, even in those with moderate renal failure. In the event of hepatic dysfunction, the dose of argatroban must be reduced. The anticoagulant effect is monitored by the aPTT.

### Table 145.4 Alternatives to Heparin for the Treatment of Heparin-Induced Thrombocytopenia

<table>
<thead>
<tr>
<th>Agent (Direct Thrombin Inhibitors)</th>
<th>Clearance</th>
<th>Therapeutic Dose</th>
<th>Therapeutic Dose</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepirudin (Refudan, Berlex)²</td>
<td>Renal</td>
<td>IV. 0.4 mg/kg of body weight (up to 110 kg); IV bolus followed by 0.15 mg/kg/hr (up to 110 kg) (maximal initial infusion, 16.5 mg/hr)</td>
<td>Measure aPTT 2 hrs after therapy started and after each dose adjustment; therapeutic range, 1.5–2.5 times the baseline value (optimal aPTT, &lt;65 s); check baseline PT before switching therapy to warfarin²</td>
<td>Bleeding with therapeutic dose in 17.6% of patients; antilepirudin antibodies develop in 30% of patients</td>
</tr>
<tr>
<td>Argatroban (Novastan, GlaxoSmithKline)²</td>
<td>Hepatic</td>
<td>2 μg/kg/min continuous infusion (maximal infusion, 10 μg/kg/min)</td>
<td>Measure aPTT 2 hrs after therapy started and after each dose adjustment; therapeutic range, 1.5–2.5 times the baseline value (optimal aPTT, &lt;65 s); check baseline PT before switching therapy to warfarin²</td>
<td>Bleeding with therapeutic dose in 17.6% of patients; antilepirudin antibodies develop in 30% of patients</td>
</tr>
<tr>
<td>Bivalirudin (Angiomax, The Medicines Company)²</td>
<td>Enzymatic (80%) and renal (20%)</td>
<td>2 μg/kg/min continuous infusion (maximal infusion, 10 μg/kg/min)</td>
<td>Measure aPTT 2 hrs after therapy started and after each dose adjustment therapeutic range, 1.5–2.5 times the baseline value (optimal aPTT, &lt;65 s); check baseline PT before switching therapy to warfarin²</td>
<td>Bleeding with therapeutic dose in 17.6% of patients; antilepirudin antibodies develop in 30% of patients</td>
</tr>
<tr>
<td>Anti-factor Xa therapy Danaparoid (Orgaran, Diosynth)²</td>
<td>Renal</td>
<td>IV. 2,250 U bolus followed by 400 U/hr for 4 hrs, then 150–200 U/hr</td>
<td>Nor required, but if needed, maintain anti-factor Xa level, 0.5–0.8 U/mL</td>
<td>Bleeding with therapeutic dose in 8.1% of patients; cross-reactivity with PF4-heparin antibodies develop in 3.2% of patients</td>
</tr>
</tbody>
</table>

aPTT, activated partial thromboplastin time; PT, prothrombin time; hr, hour; s, second.

Except where indicated, the guidelines for dosing and monitoring are from the manufacturers of the drugs. Guidelines for therapeutic dosing are for intravenous (IV) infusion, except for bivalirudin, which is used in patients undergoing percutaneous coronary intervention (PCI). The guidelines of the American College of Chest Physicians recommend overlap use of direct thrombin inhibitor therapy and warfarin therapy for more than 5 days, whereas the Hemostasis and Thrombosis Task Force of the British Committee for Standards in Haemotology recommend overlap use of direct thrombin inhibitor therapy and warfarin therapy until the international normalized ratio (INR) is at a therapeutic level for at least 48 hrs.

²These drugs have been approved in the United States for the treatment of heparin-induced thrombocytopenia.

³Thrombolytic therapy is not advised in older patients or patients with renal insufficiency.

⁴This value is the maximal aPTT recommended by Lubenow et al.

⁵Therapeutic lepirudin may prolong the baseline PT slightly, but it generally does not interfere with conversion from lepirudin to warfarin therapy. If the PT is prolonged by more than a few seconds, further evaluation should be undertaken before initiating warfarin.

⁶Combined anticoagulant therapy with argatroban and warfarin produces an INR response that is significantly greater than that obtained with warfarin alone. To change therapy from argatroban to warfarin for outpatient anticoagulant therapy, the INR should be monitored daily, and when the INR is greater than 4, the argatroban infusion should be withheld and the INR rechecked to determine whether it is therapeutic. An alternative strategy would be to use a chromogenic factor X assay to monitor warfarin therapy while the patient is also receiving argatroban.

²This drug is not available in the United States.

Lepirudin is a recombinant polypeptide originally derived from the medicinal leech (see below). It inhibits thrombin directly and is approved only for the treatment of HIT. The anticoagulant effect of lepirudin is monitored by the aPTT. It is renally excreted, and the risk for accumulation and bleeding is high in patients with renal failure; the half-life of lepirudin is 1.3 hours.

Danaparoid is a mixture of heparan sulfate, dermatan sulfate, and chondroitin sulfate; the drug reduces thrombin generation in vivo by the inhibition of factor Xa. Although no longer available in the United States, it is used for the treatment of HIT elsewhere. It is important to consider that cross-reactivity between heparin and danaparoid may occur in up to 30% of cases; in this case, a direct thrombin inhibitor should be used for treatment.

A third direct thrombin inhibitor, bivalirudin, is not approved for the treatment of HIT but has been successfully used and reported off-label for this use (113). An early transition from intravenous heparin or LMWH anticoagulation to warfarin (or an equivalent anticoagulant) has been standard therapy for most patients with acute venous and arterial thromboembolism. This approach may also help prevent HIT by limiting a patient’s total dose-time exposure to heparin medications. One complication to be considered is that early transition has been associated with further thrombotic complications of venous limb gangrene and warfarin-induced skin necrosis (112,113).

Warfarin and other equivalent vitamin K antagonists counter thrombin generation by slowly decreasing the plasma levels of the vitamin K factors (II, VII, IX, X) while concurrently decreasing the natural anticoagulant factors C and S. During the transition to oral vitamin K antagonist therapy in patients with HIT, thrombin is still being generated (warfarin having failed to control this). Due to their shorter half-lives, factors VII and protein C are reduced faster than the prothrombotic factors II, IX, and X (Table 145.5). This results in a supratherapeutic INR secondary to factor VII depletion and a transient hypercoagulable state due to the decrease in protein C without a concurrent decrease in the prothrombotic levels of factors II and X. Throughout this process, there is still increased thrombin generation due to the HIT, and venous limb gangrene and/or warfarin-induced skin necrosis may develop as a result (110,113).

In these patients, it has been recommended to use the direct thrombin inhibitors available—argatroban, lepirudin, and bivalirudin or danaparoid—once HIT has been established and discontinue the use of heparin or LMWH. Anticoagulation needs to be ensured, and with use of these alternatives, there should be no interruption in anticoagulation therapy. Oral therapy with warfarin or an equivalent vitamin K-antagonist agent should be avoided until the patient’s platelet count has recovered to near-normal levels (>150,000 platelets/μL). Thereafter, one may begin administering warfarin at modest doses (2.5 to 5.0 mg orally [PO]), titrating to and maintaining the target INR; warfarin should not be used as the initial treatment for HIT (112,113,116).

**Low-Molecular-Weight Heparin**

LMWH is prepared from UH by controlled depolymerization of the parent drug into short segments. The molecular weight of LMWH ranges from 1,000 to 10,000, and about 20% of the LMWH chains contain pentasaccharide sequences that are needed for antithrombin binding.

**Mechanism of Action**

LMWH chains bind to antithrombin and brings about conformational changes that lead to inhibition of factor Xa. The ratio of inhibition of thrombin to factor Xa varies from 1:2 to 1:4 for different preparations of LMWH (117). LMWH is being increasingly used for the treatment of venous thromboembolic disease in non-ICU patients. It can be administered as a subcutaneous injection once or twice daily and intravenously when a rapid anticoagulant effect is needed. It is as safe and effective as intravenous and subcutaneous UH (76).

The shorter chains of LMWH bind less avidly to endothelial cells, macrophages, and heparin-binding proteins and have better bioavailability (118). They tend to accumulate in vivo, leading to longer half-life, and have more predictable renal clearance and a greater ability to inactivate factor Xa compared to inactivation of thrombin and, consequently, have a negligible effect on the aPTT. The clearance of LMWH is dose independent and is accomplished almost exclusively by the kidneys; hence the drug can accumulate in renal insufficiency. LMWH has proved to be cost effective because of the reduced need for monitoring, and there are several advantages of LMWH over the UH (Table 145.6).

The disadvantages of LMWH, which may be more pertinent to the ICU, include the absence of an established dose for obese patients and impaired clearance in patients with renal failure. These can be overcome by monitoring anti–factor-Xa levels and adjusting the subsequent doses. Based on the anti–factor-Xa levels, LMWH has a plasma half-life of 4 hours. The therapeutic anti–factor Xa levels with LMWH range from

### Table 145.6: Advantages of Low-Molecular-Weight Heparin over Unfractionated Heparin

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better bioavailability and longer half-life</td>
<td>Can be given subcutaneously once or twice after subcutaneous injection daily for both prophylaxis and treatment</td>
</tr>
<tr>
<td>Dose-independent clearance</td>
<td>Simplified dosing</td>
</tr>
<tr>
<td>Predictable anticoagulant response</td>
<td>Coagulation monitoring is unnecessary in most patients</td>
</tr>
<tr>
<td>Lower risk of heparin-induced thrombocytopenia</td>
<td>Safer than heparin for short- or long-term administration</td>
</tr>
<tr>
<td>Lower risk of osteoporosis</td>
<td>Safer than heparin for extended administration</td>
</tr>
</tbody>
</table>

Hip or Knee Replacement Surgery. In patients undergoing hip or knee replacement surgery, the recommended dose of enoxaparin is 30 mg every 12 hours, administered by SC injection. Provided that hemostasis has been established, the initial dose should be given 12 to 24 hours after surgery. For hip replacement surgery, a dose of 40 mg once a day SC, given initially 12 (±3) hours prior to surgery, may be considered. Following the initial phase of thromboprophylaxis in hip replacement surgery patients, continued prophylaxis with enoxaparin 40 mg once a day administered by SC injection for 3 weeks is recommended; the usual duration of administration is 7 to 10 days.

Restricted Mobility. In medical patients at risk for thromboembolic complications due to severely restricted mobility during acute illness, the recommended dose of enoxaparin is 40 mg once a day administered by SC injection (119).

Mechanical Prosthetic Heart Valves. The use of enoxaparin has not been adequately studied for thromboprophylaxis or for long-term use in patients with mechanical prosthetic heart valves. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin for thromboprophylaxis. Some of these patients were pregnant women in whom thrombosis led to maternal and fetal deaths. Insufficient data, issues related to the underlying disease state, and the possibility of inadequate anticoagulation complicates evaluation of these cases. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism (119).

Like enoxaparin, dalteparin consists of small heparin molecules ranging from 2,000 to 9,000 daltons. It is administered subcutaneously and has better availability and a longer half-life than UFH. It has a similar mechanism of action as enoxaparin, selectively inhibiting factor Xa. The inhibitory activity is 2.7:1 compared to 1:1 for UFH. The inhibition of factor Xa prevents the formation of fibrin clots. The elimination of the drug occurs via the renal route and is dose independent, with a plasma half-life of 3 to 5 hours. Dalteparin does not significantly affect the platelet activity, prothrombin time (PT), or aPTT and has been shown to be superior to warfarin in preventing DVT following total hip replacement surgery (120). The FRISC trial (Low–Molecular-Weight Heparin [Fragmin] during Instability in Coronary Artery Disease) showed that dalteparin decreased the risk of death or AMI by 36% as compared to aspirin alone (121).

In the FRIC trial (Fragmin in Unstable Coronary Artery Disease), dalteparin was found to be as effective as intravenous heparin in preventing death or AMI in the acute phase following unstable angina or non–Q wave MI (119).

Tinzaparin is a relatively new drug with a similar mechanism of action and pharmacokinetic profile as enoxaparin and dalteparin. It was approved for the treatment of symptomatic DVT in 2000.

Complications

Bleeding. The major complication of the LMWHs is bleeding and is as frequent as with UFH. It is, of course, more common in patients receiving antiplatelet or antifibrinolytic therapy in addition to LMWH. Recent surgery, coagulopathy, or trauma also increases the risk of bleeding (99). Protamine sulfate can be used as an antidote, although it incompletely neutralizes the

### TABLE 145.7 LMWH Dosage Regimens for Patients with Severe Renal Impairment

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis in abdominal surgery</td>
<td>30 mg SC once daily</td>
</tr>
<tr>
<td>Prophylaxis in hip or knee replacement surgery</td>
<td>30 mg SC once daily</td>
</tr>
<tr>
<td>Prophylaxis in medical patients during acute illness</td>
<td>30 mg SC once daily</td>
</tr>
<tr>
<td>Prophylaxis of ischemic complications of unstable angina and non–Q wave myocardial infarction when concurrently administered with aspirin</td>
<td>1 mg/kg SC once daily</td>
</tr>
<tr>
<td>Inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin sodium</td>
<td>1 mg/kg SC once daily</td>
</tr>
<tr>
<td>Outpatient treatment of acute deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin sodium</td>
<td>1 mg/kg SC once daily</td>
</tr>
</tbody>
</table>

SC, subcutaneously.
anticoagulant activity by binding only to the longer chains of LMWH. The longer chains are responsible for the antithrombin activity, but the short chains, which inhibit factor Xa activity, will not bind to protamine sulfate, resulting in the latter’s ability to only partially reverse the effect of LMWH (122).

Thrombocytopenia. LMWH binds less avidly to platelets, causes less release of PF4, and has a reduced affinity for PF4; it is thus less likely to trigger the formation of antibodies, resulting in a lower incidence of HIT as compared to UH. Unfortunately, antibodies already formed in established HIT cases can exhibit cross-reactivity with LMWH and lead to thrombosis and other complications of this disorder (123,124); for this reason LMWHs should not be used as a substitute for heparin in HIT patients.

**Warfarin (Coumadin)**

Warfarin, an antagonist of vitamin K, prevents the vitamin K–mediated posttranslational modification of clotting factors II, VII, IX, and X, as well as the naturally occurring endogenous anticoagulant proteins C and S. These factors are biologically inactive without the carboxylation of selected glutamic acid residues, a process requiring reduced vitamin K as a cofactor.

Warfarin is well absorbed in the gut and transported in plasma bound to albumin. Therapeutic doses of warfarin reduce the production of functional vitamin K-dependent clotting factors by 30% to 50%; a concomitant reduction in the carboxylation of secreted clotting factors yields a 10% to 40% decrease in the biologic activity of the clotting factors. As a result, the coagulation system becomes functionally deficient (125).

The PT is the primary assay used in monitoring warfarin therapy. Changes in the PT noted in the first few days of warfarin therapy are primarily due to the reduction in factors VII and IX, with the shortest half-lives, 6 and 24 hours respectively. Commercially available tissue thromboplastins differ in their sensitivity to the warfarin effect; hence, PTs performed with different thromboplastins are not always directly comparable, and for this reason, the INR has been adopted using thromboplastins with international sensitivity index values near 1.0 (125).

Warfarin is used in patients with lower extremity DVT to prevent extension and to reduce the risk of PE. Patients with PE are treated with warfarin to prevent further thromboemboli. Warfarin is used in patients with atrial fibrillation and artificial heart valves to reduce the risk of embolic strokes. It is also helpful in preventing blood clot formation in certain orthopedic surgeries such as knee or hip replacements and in preventing thrombotic stenosis of coronary artery stents (Table 145.8).

The most common complication of warfarin therapy is bleeding, occurring in 6% to 39% of patients annually (126,127); the incidence of bleeding is related to the intensity of anticoagulation. As the need for intense anticoagulation has evolved and been reduced over the last 20 years, the incidence of bleeding has decreased significantly. Moderate bleeding (manifested by elevated INR) can be treated by adjusting down the warfarin dose. If severe bleeding is encountered, this can be adequately treated with fresh-frozen plasma.

| Table 145.8 Therapeutic Goals and Duration of Warfarin Anticoagulation |
|----------------|-----------------|-----------------|
| Indication | INR | Duration |
| Prophylaxis of venous thrombosis for high-risk surgery | 2–3 | Clinical Judgment |
| Treatment of venous thrombosis | | |
| First episode | 2–3 | 3–6 mo \(^a\) |
| High risk of recurrent thrombosis | 2–3 | Lifelong |
| Thrombosis associated with antiphospholipid antibody | 3–4 | Lifelong |
| Treatment of pulmonary embolism | | |
| First episode | 2–3 | 3–6 mo |
| High risk of recurrent embolism | 2–3 | Lifelong |
| Prevention of systemic embolism | | |
| Tissue heart valves | 2–3 | 3 mo |
| Acute myocardial infarction (to prevent systemic embolism) | 2–3 | Clinical Judgment |
| Valvular heart disease (after thrombotic event or dilated left) | 2–3 | Lifelong |
| Atrial fibrillation | 2–3 | Lifelong |
| Chronic or intermittent | 2–3 | 3 weeks before and 4 weeks after atrial fibrillation if normal sinus rhythm is maintained |
| Cardioversion | 2–3 | | |
| Prophylaxis of venous thrombosis | | |
| Mechanical | 2.5–3.5 \(^c\) | Lifelong |
| Bioprosthetic | 2–3 | Clinical Judgment (3 mo optional) |
| Artificial heart valves | | |
| Aortic position | | |
| Mechanical | 2.5–3.5 \(^c\) | Lifelong |
| Bioprosthetic | 2–3 | 3 mo |
| Mitral position | | |
| Mechanical | 2.5–3.5 \(^c\) | Lifelong |
| Bioprosthetic | 2–3 | 3 mo |

INR, international normalized ratio.

\(^a\)All recommendations are subject to modification by individual characteristics. First event with reversible or limited risk factors (surgery, trauma, immobilization, estrogen use).

\(^b\)Heparin antagonists are elected to prevent recurrent myocardial infarction, an INR of 2.5–3.5 is recommended.

\(^c\)Depending on the type of prosthetic valve and valve position (mitral), some patients may benefit from INR in upper therapeutic range.


**Alternative Therapies**

**Thrombin Inhibitors**

Heparin, and subsequently LMWH, in addition to warfarin have been used effectively for the treatment of both venous and arterial thromboemboli, but these drugs have drawbacks. The biophysical limitations of heparin include the inability of the heparin/antithrombin complex to inhibit factor Xa within the prothrombinase complex and thrombin bound to fibrin, clotting enzymes that are important triggers of thrombin growth (128).

Thrombin, a trypsinlike serine protease, is the enzyme that converts fibrinogen to fibrin; it may be inhibited either directly...
or indirectly. Indirect thrombin inhibitors act by catalyzing the reaction of antithrombin and/or heparin cofactor II. Thrombin has great substrate specificity secondary to its surface binding sites (e.g., exosite 1). Direct thrombin inhibitors directly bind thrombin at the exosite 1 site or the other active site of thrombin, thereby blocking this procoagulant from reacting further. Direct thrombin inhibitors do not bind PF4, and their anti-coagulant activity is unaffected by the large quantities of PF4 released in the surrounding region of platelet-rich thrombi. Additionally, direct thrombin inhibitors inactivate fibrin-bound thrombin as well as fluid-phase thrombin (128,129).

Three parenteral direct thrombin inhibitors have been approved for limited use in the United States and Canada. Hirudin and argatroban are approved for treatment of patients diagnosed with heparin-associated thrombocytopenia. Bivalirudin has been approved as an alternative therapy for heparin-sensitive patients undergoing PCIs.

**Hirudin**

This agent is a 65 amino acid polypeptide originally isolated from the salivary glands of the medicinal leech; it is now available in recombinant DNA technology (130). The recombinant form exhibits an approximate 20-fold reduced affinity for thrombin as compared to the native form of the drug (131). Hirudin directly inhibits thrombin in a bivalent manner in that the globular amino-terminal domain interacts with the active site of thrombin. The anionic carboxy-terminal tail binds to exosite 1 on thrombin, the substrate recognition site (131). The hirudin/thrombin complex is essentially irreversible. This may create a problem if significant bleeding should occur, as there is no specific antidote. Recombinant hirudin—for example, desirudin and lepirudin—have a leucine substituted for an isoleucine at the N-terminal end of the molecule. Lepirudin (Refudan) has been approved in North America for the treatment of HIT subtypes 1 and 2 (132).

The plasma half-life of hirudin is approximately 60 minutes following intravenous injection and 120 minutes following subcutaneous administration (133). It is cleared via the kidneys and should be used with caution, if at all, in patients with renal insufficiency. The anticoagulant activity can be measured using the aPTT. Dose adjustment must be made to maintain the aPTT within a therapeutic range ratio of 1.5 to 2.0 time normal, measured approximately 4 hours after drug initiation. The correlation between plasma hirudin levels and the aPTT is nonlinear, and therefore the ecarin clotting time is the more preferable means of monitoring anticoagulation. Dose adjustments need to be made in those with renal impairment. Antibodies to lepirudin develop in approximately 30% of patients following their first exposure; this number may rise to 70% following repeat exposure. Serious anaphylactic reactions have occurred following initial and subsequent exposures to lepirudin, resulting in shock and death. Therefore, patients should not be treated with this agent more than one time. Rarely, in the hirudin-treated patient, there may develop non-neutralizing hirudin antibodies that prolong its anticoagulant effect because of delayed hirudin–antibody complex clearance (131). Thus, continued close monitoring of the aPTT is needed during the course of therapy, even when the initial anticoagulant effects appear stable, to avoid the risk of bleeding.

Hirudin has been successfully used, and is licensed for, the treatment of arterial or venous thrombosis complicating heparin-induced thrombocytopenia. It has also been used in patients with HIT undergoing cardiopulmonary bypass. Hirudin has been shown to be superior to heparin or LMWHs for thromboprophylaxis in patients undergoing elective hip arthroplasty, and it does not increase the risk of bleeding in this high-risk setting. Hirudin has been used extensively in patients with ACSs and for venous thromboprophylaxis. However, because of its narrow therapeutic index and high risk of bleeding, it must be used with extreme caution and is not currently approved for this use (128).

**Desirudin**

Desirudin is a recombinant form of hirudin for subcutaneous administration; it is a direct thrombin inhibitor indicated for the prevention of DVT that puts the patient at risk for PE. It directly inhibits free and fibrin-bound thrombin (133–135), and has demonstrated improved efficacy and comparable bleeding outcomes to both UFH and enoxaparin for the prevention of thromboembolism in patients undergoing elective total hip replacement (136–138). The benefit of using a direct thrombin inhibitor over either LMWH or UFH has the advantage of minimizing the potential of developing HIT (139,140,141). The typical dose in patients with normal renal function is 15 mg subcutaneously every 12 hours following an initial dose; it is given 30 minutes prior to hip surgery or in the postoperative period. The half-life is approximately 2 hours (133,140,141).

**Bivalirudin**

This is a 20 amino acid synthetic polypeptide 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 carboxyl-terminal (142,143) dodecapeptide that interacts with exosite 1 on thrombin (139,140). Bivalirudin differs from hirudin in that, once bound to thrombin, the Arg-Pro bond on the amino-terminal extension of bivalirudin is cleaved, converting bivalirudin into a lower-affinity thrombin inhibitor, therefore producing only transient inhibition of the active site (143) of thrombin and thereby allowing recovery of thrombin activity (140). The shorter half-life of bivalirudin, 25 minutes after intravenous injection, and the fact that only about 20% is renally excreted (144), may make bivalirudin a safer alternative to hirudin. In patients with a high risk of developing HIT, bivalirudin is typically administered as a weight-adjusted (1 mg/kg) bolus dose given prior to PCIs and followed by a 4-hour infusion (0.2 to 0.5 mg/kg/hr); the dose is adjusted according to renal function. Robson et al. demonstrated that the plasma clearance of bivalirudin in patients with moderate or severe renal impairment is reduced by approximately 20% as compared to that in patients with normal or mild renal function, and suggests that bivalirudin infusion should be reduced by 20% in patients with moderate-to-severe renal impairment (144). The anticoagulant effect is monitored by the activated clotting time (ACT), and an additional bolus dose is given if the ACT is less than 350 seconds.

**Argatroban**

This is a synthetic L-arginine derivative competitive inhibitor of thrombin. Argatroban binds noncovalently to the active site of thrombin to form a reversible complex (145). The plasma half-life of this agent is 45 minutes. It is monitored using the aPTT, and the dose is adjusted to maintain a therapeutic aPTT ratio of 1.5 to 3.0. It is metabolized in the liver and needs to be used with caution in patients with hepatic dysfunction (143).
Argatroban is considered the drug of choice for patients with severe renal impairment. Therapy with this agent can prolong plasma INR more than the other direct thrombin inhibitors and may complicate overlap therapy with vitamin K antagonists. Argatroban has been approved for use in patients with documented HIT and for anticoagulation in HIT patients undergoing PCI (132).

**Melagatran/Ximelagatran**

Melagatran is a dipetide mimetic of the region of fibrinopeptide A that interacts with the active site of thrombin. This drug has poor oral bioavailability and must be given via the subcutaneous route. Ximelagatran is an uncharged lipophilic prodrug exhibiting about 20% bioavailability after oral administration. Once absorbed, ximelagatran is rapidly transformed to melagatran, which has a half-life of approximately 4 to 5 hours. The primary route of excretion for melagatran is the kidneys, where approximately 80% is eliminated. Dose adjustments may be needed in the elderly and in those patients with renal impairment. There appears to be no adverse food or drug interaction to influence the absorption of ximelagatran, and it therefore produces a predictable anticoagulant effect. The need for routine monitoring of this drug is usually unnecessary. Ximelagatran is under evaluation for thromboprophylaxis in orthopedic patients (146) and for the treatment of venous thromboembolism and atrial fibrillation (147).

**Dabigatran**

Dabigatran etexilate is an orally administered prodrug metabolized in the liver to dabigatran. This is the only orally administered, reversible direct thrombin inhibitor approved for prevention of stroke and systemic embolism in people with nonvalvular atrial fibrillation. It should not be used in patients with prosthetic heart valves or during pregnancy.

The RE-LY trial (Randomised evaluation of long-term anticoagulation therapy) compared two doses of dabigatran, 110 and 150 mg administered twice daily with warfarin for noninferiority in prevention of stroke or systemic embolus in patients with a history of atrial fibrillation. When dabigatran was compared to patients receiving warfarin and who were titrated to a therapeutic target INR of 2 to 3, both doses of the dabigatran significantly decreased the annual rate of stroke or systemic embolus, the primary outcomes, by 1.69% per year in the warfarin group, as compared with 1.53% per year in the group that received 110 mg of dabigatran (relative risk with dabigatran, 0.91; 95% confidence interval [CI], 0.74 to 1.11; p < 0.001 for noninferiority) and 1.11% per year in the group that received 150 mg of dabigatran (relative risk, 0.66; 95% CI, 0.53 to 0.82; p < 0.001 for superiority). The rate of major bleeding was 3.36% per year in the warfarin group, as compared with 2.71% per year in the group receiving 110 mg of dabigatran (p = 0.003) and 3.11% per year in the group receiving 150 mg of dabigatran (p = 0.31) (149).

Dabigatran is typically given at a fixed dose without monitoring. The maximum anticoagulant effect is achieved within 2 to 3 hours following administration. In patients with normal renal function, when administered for prevention of venous thromboembolism in surgical patients, a dose of dabigatran, 150 mg given twice daily is indicated following 5 to 10 days of parenteral anticoagulant therapy. When patients with atrial fibrillation are being treated for stroke prevention the suggested dose in patients is 150 mg taken orally twice daily (149).

Even though dabigatran has been associated with less severe bleeding than warfarin (149), life-threatening hemorrhage can occur especially during emergency surgical procedures. It has been reported that a monoclonal antibody fragment, idarucizumab, binds dabigatran with an affinity which is 350 times that observed with thrombin, neutralizing its activity (150,151). An interim analysis was reported in 2015 from the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study evaluating the safety and capacity of 5 g of intravenous idarucizumab to reverse the anticoagulant effects of dabigatran in patients who had serious bleeding or requiring an urgent intervention. This analysis demonstrated that idarucizumab was able to completely reverse anticoagulant activity in 88% to 98% of patients within minutes (152).

**Factor Xa Inhibitors**

Drugs that block factor Xa are considered as either indirect or direct inhibitors. Indirect factor Xa inhibitors act by binding to and activating antithrombin, which then inhibits free factor Xa. Direct factor Xa inhibitors actually bind to and inhibit factor Xa without requiring antithrombin to be present.

**Indirect Factor Xa Inhibitors**

Fondaparinux and idraparinux are two relatively new parenteral indirect factor Xa inhibitors. They are synthetic analogs of the antithrombin-binding pentasaccharide sequence found in heparin and LMWH. However, these drugs are modified to increase their affinity for antithrombin as compared to both heparin and LMWH. The chain length of these molecules is too short to bridge thrombin to antithrombin; therefore, these agents act by catalyzing factor Xa inhibition by antithrombin. Their properties are quite different from those of LMWH (Table 145.9).

There are potential benefits of fondaparinux over LMWH. It is synthetically produced, has a longer half-life, and does not bind to plasma proteins other than antithrombin. Additionally,
it does not bind to PF4 to form the heparin/PF4 complexes that serve as the antigenic target for the antibodies that cause heparin-induced thrombocytopenia, and may be safer to use in these patients (153,154). Fondaparinux has been extensively studied and has been found to be effective as an antithrombotic agent for the prevention and treatment of both venous and arterial disorders. It is currently approved as thromboprophylaxis following orthopedic procedures, as initial treatment for venous thromboembolism, and is being investigated as an antithrombotic agent in cardiac disease.

Idraparinux is a chemically modified analog of fondaparinux that binds to antithrombin with such a high affinity that its half-life approximates that of antithrombin (155). This drug requires subcutaneous dosing only once a week, has a long half-life and lacks an antidote. In one study, bleeding occurred in healthy volunteers, but the anticoagulant effect reversed by recombinant factor VIIa (132). The Amadeus study demonstrated that clinically relevant bleeding was evident when compared to vitamin K antagonist medication and did not appear to reduce the risk of stroke. Further development of this medication has been suspended (156).

**Direct Factor Xa Inhibitors**

Several oral acting synthetic direct factor Xa inhibitors are currently available; none are available for parenteral use. These drugs inhibit both free and activated platelet-bound factor Xa trapped within a thrombus as part of the prothrombinase complex.

Rivaroxaban is an orally active oxazolidinone derivative that reversibly inhibits factor Xa. It achieves 80% bioavailability after a single oral dose, with peak plasma levels in 2 to 3 hours and a half-life of 7 to 17 hours. It is approved for stroke prevention in atrial fibrillation and venous thromboembolism prophylaxis following orthopedic surgery, as well as treatment for acute ST-segment elevation MI and new-onset left bundle branch block. Various clinical trials have demonstrated the importance and benefit of early and full reperfusion in improving clinical outcomes following an acute MI (163–166). Rivaroxaban is also indicated in the treatment of ischemic stroke (167), cerebral vein and sinus thrombosis (168), thrombosed mechanical valves, and thrombosed arteriovenous shunts and catheters. These agents have evolved from the non–fibrin-selective first-generation agents to the more fibrin-selective third-generation agents. As there are still limitations with the currently available agents, work continues to achieve an ideal drug.

Apixaban has an identical mechanism of action and indications to rivaroxaban. It is administered orally in a dose of 5 mg twice daily. This is adjusted to 2.5 mg twice daily for patients greater than 80 years, less than 60 kg, and with renal insufficiency (creatinine >1.5 mg/dL). Similarly to rivaroxaban, it has a high oral bioavailability and short onset to peak action of 3 hours; the plasma half-life is approximately 12 hours and thus a twice daily dosing schedule is required. A dose reduction or avoidance should be considered in patients taking dual inhibitors of the cytochrome P-3A4 and P-glycoprotein (159).

The efficacy of apixaban was demonstrated in the apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (the ARISTOTLE Trial), a noninferiority trial comparing apixaban, 5 mg orally administered twice daily with warfarin (target range INR = 2–3) for the prevention of stroke and systemic embolization in atrial fibrillation in 18,206 patients followed for 12 months. Apixaban was associated with significantly lower rate of stroke and systemic embolization than warfarin (1.27% vs. 1.60%, p < 0.001). Apixaban was also associated with a significant reduction in major bleeding (2.13% vs. 3.09%, p < 0.001) (160).

**Thrombolytic Therapy**

Thrombolytic agents act as plasminogen-activating agents, catalyzing the conversion of endogenous plasminogen to plasmin. These agents will dissolve both fibrin deposits and pathologic thrombi at sites of vascular injury and, thus, may be associated with significant hemorrhage.

In the treatment of pulmonary embolus, thrombolytic therapy followed by heparin administration has been shown to be more efficacious in thromboembolus dissolution than heparin alone in the acute (first 24 hours) setting (161,162). These agents lead to a more rapid resolution of lung scan abnormalities and hemodynamic improvements, but the benefit over the longer term is questionable. Recent guidelines do not recommend thrombolysis for the treatment of DVT unless limb ischemia and limb loss is imminent (162).

Although beyond the scope of this review, thrombolytic therapy has become a standard treatment for patients presenting with acute ST-segment elevation MI and new-onset left bundle branch block. Various clinical trials have demonstrated the importance and benefit of early and full reperfusion in improving clinical outcomes following an acute MI (163–166). Thrombolytic therapy is also indicated in the treatment of ischemic stroke (167), cerebral vein and sinus thrombosis (168), thrombosed mechanical valves, and thrombosed arteriovenous shunts and catheters. These agents have evolved from the non–fibrin-selective first-generation agents to the more fibrin-selective third-generation agents. As there are still limitations with the currently available agents, work continues to achieve an ideal drug.

**First-generation thrombolytic agents** are not fibrin specific and convert circulating plasminogen to plasmin. There is constant equilibrium between circulating plasminogen and plasminogen that is in the thrombus. There is eventual depletion of plasminogen, reducing clot lysis. Additionally, the first-generation agents are associated with increased risk of allergic reaction and have comparatively short halflives.

Stereotoksinase is a single-chain polypeptide, with a molecular weight of 47 to 50.2 kD, produced by group C β-hemolytic streptococci (169). It works by binding with circulating plasminogen to form an activator complex that converts plasminogen to plasmin by proteolytic cleavage, forming a streptokinase–plasmin complex (170). This 1:1 complex has increased catalytic activity compared with plasmin. The streptokinase–plasmin complex–mediated degradation of fibrin leads to stimulation of locally bound streptokinase–plasmin and streptokinase–plasminogen complexes, which results in an acceleration in plasminogen activation and clot dissolution. In addition, streptokinase can increase levels of activated protein C, enhancing clot lysis. The
half-life of the streptokinase–plasminogen complex is approximately 23 minutes, with a lytic effect ranging from 82 to 184 minutes. There are no metabolites of streptokinase; it is eliminated by the liver (171,172).

Adverse reactions include allergic reactions—rarely anaphylaxis—and bleeding. Hypotension not related to bleeding or anaphylaxis may also be seen during streptokinase infusion in 1% to 10% of patients. For PE, the FDA recommends that streptokinase be given as a 1 million IU dose infusion over 24 hours. For acute MI, the adult dose is 1.5 million IU in 50 mL 5% dextrose in water given intravenously over 5 minutes.

Anistreplase has a longer half-life compared to streptokinase so can be used as a bolus. It is antigenic as streptokinase so repeat administration within 1 year is avoided. The lack of any compelling advantages (other than bolus administration) and cost higher than streptokinase has reduced anistreplase to an infrequently prescribed drug for acute myocardial infarction.

Urokinase is a two-chain serine protease containing 41 amino acid residues, isolated from human urine and fetal kidney cell cultures as a single-chain precursor, with a molecular weight of 54 kd. In plasma, the single-chain precursor is converted to the active two-chain urokinase plasminogen activator through limited hydrolysis by plasmin and kallikrein. The two-chain active form increases the efficacy of plasmin activation, which enhances further conversion of the single-chain precursor to the two-chain urokinase plasminogen activator form. Urokinase has a 15- to 20-minute half-life and is metabolized in the liver (173,174). Because it has a shorter half-life than streptokinase, urokinase produces a less sustained fibrinolysis. It has the same potential disadvantages—significant bleeding—as do all thrombolytics. Human-derived urokinase is no longer available in North America and has been replaced by a recombinant product.

For PE, the FDA-approved regimen of urokinase is the administration of a 4,400 IU/kg body weight loading dose, followed by an infusion of 4,400 IU/kg for 12 to 24 hours. Urokinase for acute MI is less well studied than other agents, but the most commonly used regimen is 1 to 2 million U given as an intravenous load, over 15 to 30 minutes depending on side effect profile (rigors, febrile episode).

Second-generation thrombolitics are fibrin selective and were developed with the intention to limit or avoid systemic thrombolysis. The present agents may cause a mild-to-moderate depletion in levels of circulation fibrinogen and plasminogen.

Tissue-type plasminogen activator (Alteplase), a glycoprotein of 527 amino acids, was the first recombinant tissue-type plasminogen activator (rtPA) and is identical to the native form of the drug. Native tissue plasminogen activator (tPA) is naturally synthesized and made available by vascular endothelial cells. It is the enzyme that is responsible for most of the body’s natural physiologic responses to clear and reduce excessive thrombus propagation. Tissue plasminogen activator binds fibrin with a greater affinity than streptokinase, converting plasminogen to plasmin once bound to a fibrin clot surface—hence the term “clot selective.” Fibrin provides the platform for which tPA and fibrin may interact to enhance the catalytic efficiency of the plasminogen activation of tPA. Alteplase (rtPA) is rapidly cleared from plasma, primarily by the liver, having an initial half-life of less than 5 minutes. Heparin is usually administered with alteplase due to the very short half-life of this agent and to avoid reoclusion. This drug is not antigenic and is almost never associated with allergic reactions. Alteplase is the lytic agent most commonly used for the acute treatment of myocardial ischemia (174), pulmonary embolism, and acute ischemic stroke. There are two different forms of tissue-type plasminogen activator based on the number of chains: the two-chain alteplase (recombinant) and the recombinant one-chain form.

For acute MI, this drug may be given as an accelerated infusion (over 1.5 hours) or a long infusion (>3 hours). It must be given in a 1 mg/mL concentration and be reconstituted with sterile water. The accelerated infusion of rtPA is 15 mg intravenously, followed by 0.75 mg/kg, up to 50 mg, intravenously over 60 minutes with a maximum total dose of 100 mg. This is the most common regimen used for acute MI. Alternatively, the greater than 3-hour infusion begins as a 10-mg intravenous loading dose over 2 minutes, followed by a 50-mg infusion over the first hour, and by a 20-mg/kg infusion over the next 2 hours.

Alteplase is the only drug that has been studied and approved by the FDA for use in acute ischemic stroke with a well-established time of symptom onset of less than 3 hours. Once diagnosed, and within the defined time period, it is recommended that two peripheral intravenous lines—one for rtPA infusion and one for complications that may occur from therapy—be initiated. The recommended dose of alteplase for acute ischemic stroke is 0.9 mg/kg, to a maximum of 90 mg, infused over 60 minutes; 10% of the total dose is to be administered as an initial intravenous bolus over 1 minute (175).

The FDA-approved regimen for thrombolysis of PE is 100 mg of rtPA given as a continuous infusion over 2 hours: an initial 15-mg intravenous loading dose is followed by 85 mg over 2 hours. Heparin has been shown to improve the clinical course in hemodynamically stable patients with acute massive PE when receiving rtPA. Given the short half-life of the drug, if the patient can tolerate it, it would seem beneficial to administer alteplase with heparin (176).

Third-generation thrombolitics are based on modifications of the tPA structure. These modifications may give the agents longer half-lives, increased resistance to plasma protease inhibitors, and/or cause more selective binding to fibrin.

Reteplase (rtPA) is a synthetic, nonglycosylated deletion-mutant form of tPA containing 355 of the 527 amino acids of native tPA; the drug is produced in Escherichia coli via recombinant technology. Reteplase binds fibrin five times less avidly than native tissue plasminogen activator, thus allowing the drug to diffuse through the clot rather than just binding to the surface as is the mechanism of tissue plasminogen activator. In high concentrations, reteplase does not compete with plasminogen for fibrin-binding sites, but rather it allows plasminogen at the clot to be converted into plasmin. These reasons may explain why reteplase results in faster clot resolution in contrast to alteplase.

Reteplase is more rapidly cleared from plasma and has a somewhat extended half-life—11 to 19 minutes—than does alteplase. Reteplase undergoes primarily renal and some hepatic clearance; the agent is not antigenic and is rarely associated with allergic reactions. It must not be given with heparin due to physical incompatibility (176).

In the setting of acute MI, the FDA has approved the adult dose of reteplase to be two intravenous loads of 10 U each. Each loading dose is to be given over 2 minutes, with the second loading dose given 30 minutes following the first (176). Although approved by the FDA only for use in the setting of acute MI, reteplase has achieved wide off-label use for acute
Tenecteplase was approved as a fibrinolytic agent by the FDA in 2000. It is a genetically engineered mutation of tPA with a similar mechanism of action to alteplase. It is produced by recombinant technology using Chinese hamster ovary cells with a similar mechanism of action to alteplase. It is produced by recombinant technology using Chinese hamster ovary cells as a 527 amino acid glycoprotein, with several modifications by recombinant technology using Chinese hamster ovary cells. As a result, tenecteplase has a reduced sensitivity to plasminogen activator inhibitor (165), decreased plasma clearance, a 15- to 19-minute half-life, a molecular weight of 47,000, and greater fibrin specificity, which may lead to a reduction in hemorrhagic complications (177). Tenecteplase is administered as a 30- to 50-mg intravenous bolus over 5 seconds; the dose is calculated as follows: 0.5 mg/kg (166). The drug is currently under investigation for use in ischemic stroke.

Thrombolytic agents differ in their ability to cause clot lysis, as well as fibrin selectivity, and their ability to activate thrombosis and platelet aggregation. The clinical effectiveness of the same agent can be altered by dose, route of administration, and concomitant use of adjunctive agents. All thrombolytic agents are administered via the intravenous route in dosing regimens designed to achieve greater than 90% activation of the fibrinolytic system (178) (Table 145.10).

### Key Points

- The coagulation cascade is regulated by the TF pathway inhibitor, the protein C pathway, and the fibrinolytic degradation of fibrin.
- UH has been used in multiple clinical scenarios including prevention of venous thromboembolism, treatment of DVT and pulmonary embolism, and ACSs. Until recently, it has been the most widely used antithrombotic agent, although it has several disadvantages.
- The most efficient and safe method for initiating intravenous heparin therapy is using weight-adjusted nomograms.
- A single dose of aspirin is sufficient to inhibit platelet function for the life span of the platelets (30).
- Clopidogrel is more effective than aspirin in reducing atherosclerotic events, including MI, stroke, and peripheral vascular disease (45).
- The incidence of bleeding is higher among patients taking antiplatelet agents, requiring urgent surgical procedures (47).
- In the event of bleeding, the antiplatelet agent must be stopped, and platelet transfusion will be required to normalize platelet function.
- LMWH inhibits predominantly factor Xa to produce its anticoagulant effect. It can be administered as a subcutaneous injection once or twice a day.
- LMWH has proved to be cost effective as compared to UH because of reduced need for monitoring.
- LMWH tends to accumulate in patients with renal failure.
- There is no rapid and complete antagonist to the anticoagulant effects of LMWH, which may complicate ICU and surgical procedures (7).
- Direct thrombin inhibitors directly bind thrombin, thereby blocking its procoagulant effect. This class of drugs may be advantageous over indirect thrombin inhibitors such as heparin because they do not bind plasma proteins and produce a more predictable response.
• Drugs that block factor Xa are considered either indirect or direct inhibitors. Indirect agents act by binding to and activating antithrombin, which inhibits free factor Xa. Direct factor Xa inhibitors bind to and inhibit free factor and inactivate factor Xa bound to platelets.

• Thrombolytic agents act as plasminogen-activating agents, catalyzing the conversion of endogenous plasminogen to plasmin. These agents will dissolve both fibrin deposits and pathologic thrombi at sites of vascular injury and thus may be associated with significant hemorrhage.

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