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123 Antiplatelet, Anticoagulant, and Fibrinolytic Drugs

risk remains low (1 in 6000). The relative risk of VTE among pregnant or postpartum women is 4.3, and the overall incidence (absolute risk) is 199.7 per 100,000 woman-years. ■ ■GENETICS OF VENOUS THROMBOSIS (See Table 122-2) Less common causes of venous thrombosis are those due to genetic variants. These abnormalities include loss-of-function mutations of endogenous anticoagulants as well as gain-of-function mutations of procoagulant proteins. Heterozygous antithrombin defi ciency and homozygosity of the factor V Leiden mutation significantly increase the risk of venous thrombosis. While homozygous protein C or protein S deficiencies are rare and may lead to fatal purpura fulmi nans, heterozygous deficiencies are associated with a moderate risk of thrombosis. Activated protein C impairs coagulation by proteolytic degradation of FVa. Patients resistant to the activity of activated protein C may have a point mutation in the FV gene, a mutant denoted factor V Leiden. Mildly increased risk has been attributed to elevated levels of procoagulant factors, as well as low levels of tissue factor pathway inhibitor. Polymorphisms of methylene tetrahydrofolate reductase as well as hyperhomocysteinemia have been shown to be independent risk factors for venous thrombosis, as well as arterial vascular disease; however, many of the initial descriptions of genetic variants and their associations with thromboembolism are being questioned in larger, more contemporary studies. ■ ■FIBRINOLYSIS AND THROMBOSIS Specific abnormalities in the fibrinolytic system have been associated with enhanced thrombosis. Factors such as elevated levels of tissue plasminogen activator (tPA) and plasminogen activator inhibitor type 1

(PAI-1) have been associated with decreased fibrinolytic activity and an increased risk of arterial thrombotic disease. Specific genetic vari ants have been associated with decreased fibrinolytic activity, including the 4G/5G insertion/deletion polymorphism in the (plasminogen acti vator type 1) PAI-1 gene. Additionally, the 311-bp Alu insertion/dele tion in tPA’s intron 8 has been associated with enhanced thrombosis; however, genetic abnormalities have not been associated consistently with altered function or tPA levels, raising questions about the relevant pathophysiologic mechanism. Thrombin-activatable fibrinolysis inhib itor (TAFI) is a carboxypeptidase that regulates

fibrinolysis; elevated plasma TAFI levels have been associated with an increased risk of both DVT and cardiovascular disease. The metabolic syndrome also is accompanied by altered fibrinolytic activity. This syndrome, which comprises abdominal fat (central obe sity), altered glucose and insulin metabolism, dyslipidemia, and hyper tension, has been associated with atherothrombosis. The mechanism for enhanced thrombosis appears to be due both to altered platelet function and to a procoagulant and hypofibrinolytic state. One of the most frequently documented prothrombotic abnormalities reported in this syndrome is an increase in plasma levels of PAI-1. In addition to contributing to platelet function, inflammation plays a role in both coagulation-dependent thrombus formation and throm bus resolution. Both polymorphonuclear neutrophils and monocytes/ macrophages contribute to multiple overlapping thrombotic func tions, including fibrinolysis, chemokine and cytokine production, and phagocytosis. THE DISTINCTION BETWEEN ARTERIAL AND VENOUS THROMBOSIS Although there is overlap, venous thrombosis and arterial thrombosis are initiated differently, and clot formation progresses by somewhat distinct pathways. In the setting of stasis or states of hypercoagulability, venous thrombosis is activated with the initiation of the coagulation cascade primarily due to exposure of tissue factor; this leads to the formation of thrombin and the subsequent conversion of fibrinogen to fibrin. In the artery, thrombin formation also occurs, but thrombosis is primarily promoted by the adhesion of platelets to an injured vessel and stimulated by exposed extracellular matrix (Figs. 122-1 and 122-2). There is wide variation in individual responses to vascular injury, an important determinant of which is the predisposition an individual

has to arterial or venous thrombosis. This concept has been supported indirectly in prothrombotic animal models in which there is poor correlation between the propensity to develop venous versus arterial thrombosis.

Despite considerable progress in elucidating the role of hyperco agulable states in VTE, the contribution of hypercoagulability to arte rial vascular disease is much less well understood. Although specific thrombophilic conditions, such as factor V Leiden and the prothrom bin G20210A mutation, are risk factors for DVT, PE, and other VTE events, their contribution to arterial thrombosis is less well defined. In fact, to the contrary, many of these thrombophilic factors have not been found to be clinically important risk factors for arterial thrombotic events, such as acute coronary syndromes. Clinically, although the pathophysiology is distinct, arterial and venous thrombosis do share common risk factors, including age, obesity, cigarette smoking, diabetes mellitus, arterial hypertension, hyperlipidemia, and metabolic syndrome. Select genetic variants, including those of the glutathione peroxidase-3 (GPx3) gene, have also been associated with arterial and venous thrombo-occlusive disease. Importantly, arterial and venous thrombosis may both be triggered by pathophysiologic stimuli responsible for activating inflammatory and oxidative pathways. CHAPTER 123 The diagnosis and treatment of ischemic heart disease are dis cussed in Chap. 284. Stroke diagnosis and management are dis cussed in Chap. 318. The diagnosis and management of DVT and PE are discussed in Chap. 290. ■ ■FURTHER READING Ackermann M et al: Pulmonary vascular endothelialitis, thrombosis, Antiplatelet, Anticoagulant, and Fibrinolytic Drugs
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Antiplatelet,

Anticoagulant, and

Fibrinolytic Drugs Thromboembolic disorders are major causes of morbidity and mortal ity. Thrombosis can occur in arteries or veins. Arterial thrombosis is the most common cause of acute myocardial infarction (MI), ischemic stroke, and limb gangrene. VTE encompasses DVT, which can lead to postthrombotic syndrome, and PE, which can be fatal or can result in chronic thromboembolic pulmonary hypertension. Most arterial thrombi are superimposed on disrupted atheroscle rotic plaque because plaque rupture exposes thrombogenic material in the core to the blood. This material then triggers platelet aggregation and fibrin formation, which results in the generation of a platelet-rich thrombus that can temporarily or permanently occlude blood flow. In contrast, venous thrombi rarely form at sites of obvious vascular

Antithrombotic Drugs Anticoagulants Fibrinolytic agents Antiplatelet drugs FIGURE 123-1 Classification of antithrombotic drugs. disruption. Although they can develop after surgical trauma to veins or secondary to indwelling venous catheters, venous thrombi usually originate in the valve cusps of the deep veins of the calf or in the mus cular sinuses. Sluggish blood flow reduces the oxygen supply to the avascular valve cusps. Endothelial cells lining these valve cusps become activated and express adhesion molecules on their surface. Tissue factor– bearing leukocytes and microvesicles adhere to these activated cells and induce coagulation. DNA extruded from neutrophils forms neutrophil extracellular traps (NETs) that provide a scaffold that binds platelets, promotes their activation and aggregation, and activates factor XII. Local thrombus formation is exacerbated by reduced clearance of acti vated clotting factors because of impaired blood flow. If the thrombi extend from the calf veins into the popliteal and more proximal veins of the leg, thrombus fragments can dislodge, travel to the lungs, and produce PE. PART 4 Oncology and Hematology Arterial and venous thrombi are composed of platelets, fibrin, and trapped red blood cells, but the proportions differ. Arterial thrombi are rich in platelets because of the high shear in the injured arteries. In contrast, venous thrombi, which form under low shear conditions, contain relatively few platelets and are predominantly composed of fibrin and trapped red cells. Because of the predominance of platelets, arterial thrombi appear white, whereas venous thrombi are red in color, reflecting the trapped red cells. Antithrombotic drugs are used for the prevention and treatment of thrombosis. Targeting the components of thrombi, these agents include (1) antiplatelet drugs, (2) anticoagulants, and (3) fibrinolytic agents (Fig. 123-1). With the predominance of platelets in arterial thrombi, strategies to attenuate arterial thrombosis focus mainly on antiplatelet agents, although, in the acute setting, they may include anticoagulants and fibrinolytic agents. The addition of low-dose rivaroxaban, an oral factor Xa inhibitor, to dual-antiplatelet therapy reduces recurrent ischemic events and stent thrombosis in patients with acute coronary syndrome, whereas its addition to aspirin reduces the risk of major adverse coronary and limb events in patients with stable coronary or peripheral artery disease. These findings highlight the utility of combining low-dose anticoagulants with antiplatelet agents for secondary prevention

in patients at high risk for recurrent atherothrombotic events. Anticoagulants are the mainstay of prevention and treatment of VTE because fibrin is the predominant component of venous thrombi. Antiplatelet drugs are less effective than anticoagulants in this setting because of the limited platelet content of venous thrombi. Fibrinolytic therapy is used in selected patients with VTE. For example, patients with massive PE can benefit from systemic or catheter-directed fibri nolytic therapy. Pharmaco-mechanical therapy is also used to restore blood flow in patients with extensive DVT involving the iliac and/or femoral veins. ANTIPLATELET DRUGS ■ ■ROLE OF PLATELETS IN ARTERIAL THROMBOSIS In healthy vasculature, circulating platelets are maintained in an inac tive state by nitric oxide (NO) and prostacyclin released by endothelial cells lining the blood vessels. In addition, endothelial cells also express CD39 on their surface, a membrane-associated ecto-adenosine diphos phatase (ADPase) that degrades ADP released from activated platelets. When the vessel wall is damaged, the release of these substances is impaired and the subendothelial matrix is exposed. Platelets adhere to exposed collagen via α2β1 and glycoprotein (Gp) V1 and to von

Vascular Injury Exposure of collagen and VWF Tissue factor exposure Platelet adhesion and release Activation of coagulation Platelet recruitment and activation Thrombin generation Platelet aggregation Fibrin formation Platelet-fibrin thrombus FIGURE 123-2 Coordinated role of platelets and the coagulation system in thrombogenesis. Vascular injury simultaneously triggers platelet activation and aggregation and activation of the coagulation system. Platelet activation is initiated by exposure of subendothelial collagen and von Willebrand factor (VWF), onto which platelets adhere. Adherent platelets become activated and release ADP and thromboxane A2, platelet agonists that activate ambient platelets and recruit them to the site of injury. When platelets are activated, glycoprotein IIb/IIIa on their surface undergoes a conformational change that enables it to ligate fibrinogen and/or VWF and mediate platelet aggregation. Coagulation is triggered by tissue factor exposed at the site of injury. Tissue factor triggers thrombin generation. As a potent platelet agonist, thrombin amplifies platelet recruitment to the site of injury. Thrombin also converts fibrinogen to fibrin, and the fibrin strands then weave the platelet aggregates together to form a platelet/fibrin thrombus. Willebrand factor (VWF) via Gp Ibα—receptors that are constitutively expressed on the platelet surface. Adherent platelets undergo a change in shape, secrete ADP from their dense granules, and synthesize and release thromboxane A2. Released ADP and thromboxane A2, which are platelet agonists, activate ambient platelets and recruit them to the site of vascular injury (Fig. 123-2). Disruption of the vessel wall also exposes tissue factor–expressing cells to the blood. Tissue factor binds to factor VII and induces its activation, and the tissue factor–factor VIIa complex then initiates coagulation. Activated platelets potentiate coagulation by providing a negatively charged surface that binds clotting factors and supports the assembly of activation complexes that enhance thrombin generation. In addition to converting fibrinogen to fibrin, thrombin serves as a potent platelet agonist and recruits more platelets to the site of vascular injury. Thrombin also amplifies its generation by feedback activation of factors V, VIII, and XI and solidifies the fibrin network by activating factor XIII, which then cross-links the fibrin strands and renders them more resistant to degradation. When platelets are activated, Gp IIb/IIIa, the most abundant recep tor on the platelet surface, undergoes a conformational change that enables it to bind fibrinogen and, under high shear conditions, VWF. Divalent fibrinogen or multivalent VWF molecules bridge adjacent platelets together to form platelet aggregates. Fibrin strands, generated through the action of thrombin, then weave these aggregates together to form a platelet-rich fibrin clot. Antiplatelet drugs target various steps in this process. The com monly used antiplatelet drugs include aspirin, ADP receptor inhibitors, which include thienopyridines

(clopidogrel and prasugrel) as well as ticagrelor and cangrelor, dipyridamole, Gp IIb/IIIa antagonists, and vorapaxar. ■ ■ASPIRIN The most widely used antiplatelet agent worldwide is aspirin. As a cheap and effective antiplatelet drug, aspirin serves as the foundation of most antiplatelet strategies. Mechanism of Action Aspirin produces its antithrombotic effect by irreversibly acetylating and inhibiting platelet cyclooxygenase

Plaque Disruption Tissue factor Collagen VWF Platelet adhesion and secretion Aspirin COX-1 Clopidogrel Prasugrel Ticagrelor Cangrelor TXA2 ADP Platelet recruitment and activation Thrombin Vorapaxar GpIIb/IIIa activation Abciximab Eptifibatide Tirofiban Platelet aggregation FIGURE 123-3 Site of action of antiplatelet drugs. Aspirin inhibits thromboxane A2 (TXA2) synthesis by irreversibly acetylating cyclooxygenase-1 (COX-1). Reduced TXA2 release attenuates platelet activation and recruitment to the site of vascular injury. Clopidogrel and prasugrel irreversibly block P2Y12, a key ADP receptor on the platelet surface; cangrelor and ticagrelor are reversible inhibitors of P2Y12. Abciximab, eptifibatide, and tirofiban inhibit the final common pathway of platelet aggregation by blocking fibrinogen and von Willebrand factor (VWF) binding to activated glycoprotein (Gp) IIb/IIIa. Vorapaxar inhibits thrombin-mediated platelet activation by targeting protease-activated receptor-1 (PAR-1), the major thrombin receptor on human platelets. (COX)-1 (Fig. 123-3), a critical enzyme in the biosynthesis of throm boxane A2. At high doses (~1 g/d), aspirin also inhibits COX-2, an inducible COX isoform found in endothelial cells and inflammatory cells. In endothelial cells, COX-2 initiates the synthesis of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation. Indications Aspirin is widely used for secondary prevention of car diovascular events in patients with established coronary artery, cerebral artery, or peripheral artery disease. Compared with placebo in this setting, aspirin produces a 25% reduction in the risk of cardiovascular death, MI, or stroke. Aspirin is no longer used routinely for primary prevention because recent studies suggest that the risk of gastrointesti nal and intracerebral hemorrhage outweigh the benefits. Consequently, aspirin is only recommended for primary cardiac prevention if the baseline cardiovascular risk is at least 1% per year over 10 years and patients are at low risk for bleeding. Dosages Aspirin is usually administered at doses of 75–325 mg once daily. Higher doses of aspirin are not more effective than lower aspirin doses, and some analyses suggest reduced efficacy with higher doses. Because the side effects of aspirin are dose-related, daily aspirin doses of 75–100 mg are recommended for most indications. When rapid platelet inhibition is required, an initial aspirin dose of at least 160 mg should be given. Side Effects The most common side effects are gastrointestinal and range from dyspepsia to erosive gastritis or peptic ulcers with bleeding and perforation. These side effects are dose related. Use of entericcoated or buffered aspirin in place of plain aspirin does not eliminate gastrointestinal side effects. The overall risk of major bleeding with aspirin is 1–3% per year. The risk of bleeding is increased two- to threefold when aspirin is given in conjunction with other antiplatelet drugs, such as clopidogrel or ticagrelor, or with anticoagulants, such as warfarin. When dual or triple therapy is prescribed, low-dose aspirin should be given (75–100 mg daily). Eradication of Helicobacter pylori infection and administration of proton pump inhibitors may reduce the risk of aspirin-induced upper gastrointestinal bleeding in patients with peptic ulcer disease.

Aspirin should not be administered to patients with a history of aspirin allergy characterized by bronchospasm. This problem occurs in ~0.3% of the general population but is more common in those with chronic urticaria or asthma, particularly in individuals with nasal pol yps or chronic rhinitis. Hepatic and renal toxicity are observed with aspirin overdose.

Aspirin Resistance Clinical aspirin resistance is defined as the failure of aspirin to protect patients from ischemic vascular events. This is not a helpful definition because it is made after the event occurs. Fur thermore, it is not realistic to expect aspirin, which only blocks throm boxane A2–induced platelet activation, to prevent all vascular events. Aspirin resistance has also been described biochemically as a fail ure of the drug to produce its expected inhibitory effects on tests of platelet function, such as thromboxane A2 synthesis or arachidonic acid–induced platelet aggregation. Potential causes of aspirin resistance include poor compliance, reduced absorption, drug-drug interaction with ibuprofen, and overexpression of COX-2. Unfortunately, the tests for aspirin resistance have not been well standardized, and there is little evidence that they identify patients at increased risk of recurrent vascu lar events, or that resistance can be reversed by giving higher doses of aspirin or by adding other antiplatelet drugs. Until such information is available, testing for aspirin resistance remains a research tool. CHAPTER 123 ■ ■ADP RECEPTOR ANTAGONISTS The ADP receptor antagonists include the thienopyridines (clopidogrel and prasugrel) as well as ticagrelor and cangrelor. All these drugs target P2Y12, the key ADP receptor on platelets. Antiplatelet, Anticoagulant, and Fibrinolytic Drugs
Thienopyridines • MECHANISM OF ACTION The thienopyridines are structurally related drugs that selectively inhibit ADP-induced platelet aggregation by irreversibly blocking P2Y12 (Fig. 123-3). Clopi dogrel and prasugrel are prodrugs that require metabolic activation by the hepatic cytochrome P450 (CYP) enzyme system. Prasugrel is about 10-fold more potent than clopidogrel and has a more rapid onset of action because of better absorption and more streamlined metabolic activation. INDICATIONS When compared with aspirin in patients with recent ischemic stroke, recent MI, or a history of peripheral arterial disease, clopidogrel reduced the risk of cardiovascular death, MI, and stroke by 8.7%. Therefore, clopidogrel is more effective than aspirin but is also more expensive. Clopidogrel and aspirin are often combined to capi talize on their capacity to block complementary pathways of platelet activation. For example, the combination of aspirin plus clopidogrel is recommended for at least 4 weeks after implantation of a bare metal stent in a coronary artery and at least a year in those with a drug-eluting stent. Concerns about late in-stent thrombosis with drug-eluting stents have led some experts to recommend long-term use of clopidogrel plus aspirin for the latter indication. The course of dual-antiplatelet therapy is often shortened in patients at high risk of bleeding with the dropping of aspirin and continuation of the P2Y12 inhibitor. The combination of clopidogrel and aspirin is effective in patients with non-ST-segment elevation MI. Thus, in 12,562 such patients, the risk of cardiovascular death, MI, or stroke was 9.3% in those random ized to the combination of clopidogrel and aspirin and 11.4% in those given aspirin alone. This 20% relative risk reduction with combination therapy was highly statistically significant. However, combining clopi dogrel with aspirin increases the risk of major bleeding to about 2% per year. This bleeding risk persists even if the daily dose of aspirin is ≤100 mg. Therefore, the combination of clopidogrel and aspirin should only be used when there is a clear benefit. For example, this combina tion was not proven to be superior to clopidogrel alone in patients with acute ischemic stroke or to aspirin alone for primary prevention in those at risk for cardiovascular events. Prasugrel was compared with clopidogrel in 13,608 patients with acute coronary syndrome who were scheduled to undergo percutaneous coronary intervention. The incidence of the primary efficacy endpoint, a composite of cardiovascular death, MI, or stroke, was significantly lower with prasugrel than with clopidogrel (9.9% and 12.1%, respectively),

mainly reflecting a reduction in nonfatal MI. The incidence of stent thrombosis also was significantly lower with prasugrel than with clopidogrel (1.1% and 2.4%, respectively). However,

these advantages were at the expense of significantly higher rates of fatal bleeding (0.4% and 0.1%, respectively) and life-threatening bleeding (1.4% and 0.9%, respectively) with prasugrel. Because patients older than 75 years of age and those with a history of prior stroke or transient ischemic attack are at high risk of bleeding, prasugrel should generally be avoided in older patients, and the drug is contraindicated in those with a history of cere brovascular disease. Caution is required if prasugrel is used in patients weighing <60 kg or in those with renal impairment.

When prasugrel was compared with clopidogrel in 7243 patients with unstable angina or MI without ST-segment elevation, prasugrel failed to reduce the rate of the primary efficacy endpoint, which was a composite of cardiovascular death, MI, and stroke. Because of the neg ative results of this study, prasugrel is reserved for patients undergoing percutaneous coronary intervention. In this setting, prasugrel is usually given in conjunction with aspirin. To reduce the risk of bleeding, the daily aspirin dose should be ≤100 mg. For patients with noncardioembolic stroke or high-risk transient ischemic attack, the combination of clopidogrel or ticagrelor plus aspi rin for 21–30 days followed by aspirin alone thereafter reduces the risk of stroke, MI, and vascular death by up to 30% compared with aspirin alone. Therefore, dual antiplatelet therapy is often administered for the first 3–4 weeks in such patients. PART 4 Oncology and Hematology DOSING Clopidogrel is given once daily at a dose of 75 mg. Loading doses of clopidogrel are given when rapid ADP receptor blockade is desired. For example, patients undergoing coronary stenting are often given a loading dose of 300–600 mg, which produces inhibition of ADP-induced platelet aggregation in about 4–6 h. After a loading dose of 60 mg, prasugrel is given once daily at a dose of 10 mg. Patients older than age 75 years or weighing <60 kg should receive a lower daily prasugrel dose of 5 mg. SIDE EFFECTS The most common side effect of clopidogrel and prasugrel is bleeding. Because of its greater potency, bleeding is more common with prasugrel than with clopidogrel. To reduce the risk of bleeding, clopidogrel and prasugrel should be stopped 5–7 days before major surgery. In patients taking clopidogrel or prasugrel who present with serious bleeding, platelet transfusion may be helpful. Hematologic side effects, including neutropenia, thrombocytopenia, and thrombotic thrombocytopenic purpura, are rare. THIENOPYRIDINE RESISTANCE The capacity of clopidogrel to inhibit ADP-induced platelet aggregation varies among subjects. This vari ability reflects, at least in part, genetic polymorphisms in the CYP iso enzymes involved in the metabolic activation of clopidogrel. The most important of these is CYP2C19. Clopidogrel-treated patients who are homozygous for the loss-of-function CYP2C192 allele exhibit reduced platelet inhibition compared with those with the wild-type CYP2C19 allele and experience a higher rate of cardiovascular events. This is important because estimates suggest that up to 25% of whites, 30% of African Americans, and 50% of Asians carry the loss-of-function allele, which would render them resistant to clopidogrel. Even patients with the reduced-function CYP2C19 alleles may derive less benefit from clopidogrel than those with the full-function CYP2C19 allele. Con comitant administration of clopidogrel with proton pump inhibitors, which are inhibitors of CYP2C19, produces a small reduction in the inhibitory effects of clopidogrel on ADP-induced platelet aggregation. The extent to which this interaction increases the risk of cardiovascular events remains controversial. In contrast to their effect on the metabolic activation of clopidogrel, CYP2C19 polymorphisms appear to be less important determinants of the activation of prasugrel. Thus, no association was detected between the loss-of-function allele and decreased platelet inhibition or increased rate of cardiovascular events with prasugrel. The observation that genetic polymorphisms affecting clopidogrel absorption or metab olism influence clinical outcomes raised the possibility that pharmaco genetic

profiling might be useful for identifying clopidogrel-resistant

patients and that point-of-care assessment of the extent of clopidogrelinduced platelet inhibition may help detect patients at higher risk for subsequent cardiovascular events. Clinical trials designed to evaluate these possibilities have thus far been negative. Although administra tion of higher doses of clopidogrel can overcome a reduced response to clopidogrel, the clinical benefit of this approach is uncertain. Instead, prasugrel or ticagrelor may be better choices for these patients. Ticagrelor As an orally active inhibitor of P2Y12, ticagrelor differs from the thienopyridines in that ticagrelor does not require metabolic activation and it produces reversible inhibition of the ADP receptor. MECHANISM OF ACTION Like the thienopyridines, ticagrelor inhibits P2Y12. Because it does not require metabolic activation, ticagrelor has a more rapid onset and offset of action than clopidogrel, and it produces greater and more predictable inhibition of ADP-induced platelet aggre gation than clopidogrel. INDICATIONS Ticagrelor is indicated for the secondary prevention of atherothrombotic events in patients with an acute coronary syndrome treated medically or with percutaneous coronary intervention (PCI) with or without stent implantation or with coronary artery bypass graft (CABG) surgery. Ticagrelor is also indicated for up to 3 years for sec ondary prevention in patients with a prior history of MI at least 1 year ago who are at high risk for atherothrombotic events. For patients with acute coronary syndrome undergoing PCI, guidelines give preference to ticagrelor over clopidogrel, particularly in higher risk patients. DOSING Ticagrelor is initiated with an oral loading dose of 180 mg followed by 90 mg twice daily. The dose does not require adjustment in patients with renal impairment, but the drug should be used with caution in patients with hepatic disease and in those receiving potent inhibitors or inducers of CYP3A4 because ticagrelor is metabolized in the liver via CYP3A4. Ticagrelor is usually administered in conjunction with aspirin; the daily aspirin dose should not exceed 100 mg. SIDE EFFECTS In addition to bleeding, the most common side effects of ticagrelor are dyspnea, which can occur in up to 15% of patients, and asymptomatic ventricular pauses. The dyspnea, which tends to occur soon after initiating ticagrelor, is usually self-limiting and mild in intensity. The mechanism responsible for this side effect is unknown. To reduce the risk of bleeding, ticagrelor should be stopped at least 5 days before major surgery. Platelet transfusion is unlikely to be of benefit in patients with ticagrelor-related bleeding or those requiring urgent surgery because the drug will bind to P2Y12 on the transfused platelets. Bentracimab, an antibody fragment that binds ticagrelor and its metabolite with high affinity and rapidly reverses their platelet inhibitory effects, is under development for ticagrelor reversal before urgent surgery or intervention or for patients with serious bleeding. Cangrelor Cangrelor is a rapidly acting reversible inhibitor of P2Y12 that is administered intravenously. It has an immediate onset of action, a half-life of 3–5 min, and an offset of action within an hour. Cangrelor is licensed for use in patients undergoing PCI and produces rapid ADP receptor blockade in those who have not received pretreatment with clopidogrel, prasugrel, or ticagrelor. Cangrelor is administered as a 30 μg/kg IV bolus before PCI fol lowed by an infusion of 4 μg/kg per minute for at least 2 h or for the duration of the procedure, whichever is longer. When transitioning to oral P2Y12 inhibitor therapy, ticagrelor can be given at a loading dose of 180 mg at any time during the cangrelor infusion or immediately after discontinuation. In contrast, loading doses of prasugrel or clopidogrel (60 and 600 mg, respectively) should only be given after cangrelor is stopped because cangrelor blocks the interaction of their active metabolites with P2Y12. ■ ■DIPYRIDAMOLE Dipyridamole is a relatively weak antiplatelet agent on its own, but an extended-release formulation of dipyridamole combined with lowdose aspirin, a preparation known as Aggrenox, is sometimes used for secondary

prevention in patients with transient ischemic attacks or ischemic stroke.

MECHANISM OF ACTION By inhibit ing phosphodiesterase, dipyridamole blocks the breakdown of cyclic adenos ine monophosphate (AMP). Increased levels of cyclic AMP reduce intracellular calcium and inhibit platelet activation. Dipyridamole also blocks the uptake of adenosine by platelets and other cells. This produces a further increase in local cyclic AMP levels because the platelet adenosine A2 receptor is coupled to adenylate cyclase (Fig. 123-4). Platelet INDICATIONS Dipyridamole plus aspirin was compared with aspirin or dipyridamole alone, or with placebo, in patients with an ischemic stroke or transient ischemic attack. The combina tion reduced the risk of stroke by 22.1% compared with aspirin and by 24.4% compared with dipyridamole. A sec ond trial compared dipyridamole plus aspirin with aspirin alone for secondary prevention in patients with ischemic stroke. Vascular death, stroke, or MI occurred in 13% of patients given com bination therapy and in 16% of those treated with aspirin alone. Another trial randomized 20,332 patients with noncardioembolic ischemic stroke to either Aggrenox or clopi dogrel. The primary efficacy endpoint of recurrent stroke occurred in 9.0% of those given Aggrenox and in 8.8% of patients treated with clopidogrel. Although this difference was not statistically significant, the study failed to meet the prespecified margin to claim noninferior ity of Aggrenox relative to clopidogrel. These results have dampened enthusiasm for the use of Aggrenox. FIGURE 123-4 Mechanism of action of dipyridamole. Dipyridamole increases levels of cyclic AMP (cAMP) in platelets by (1) blocking the reuptake of adenosine and (2) inhibiting phosphodiesterase-mediated cyclic AMP degradation. By promoting calcium uptake, cyclic AMP reduces intracellular levels of calcium. This, in turn, inhibits platelet activation and aggregation. Because of its vasodilatory effects and the paucity of data supporting the use of dipyridamole in patients with symptomatic coronary artery disease, Aggrenox should not be used for stroke prevention in such patients. Clopidogrel is a better choice in this setting. DOSING Aggrenox is given twice daily. Each capsule contains 200 mg of extended-release dipyridamole and 25 mg of aspirin. SIDE EFFECTS Because dipyridamole has vasodilatory effects, it must be used with caution in patients with coronary artery disease. Gastroin testinal complaints, headache, facial flushing, dizziness, and hypoten sion can also occur. These symptoms often subside with continued use of the drug. ■ ■GP IIB/IIIA RECEPTOR ANTAGONISTS As a class, parenteral Gp IIb/IIIa receptor antagonists have a niche in patients with acute coronary syndrome. The three agents in this class are abciximab, eptifibatide, and tirofiban. However, abciximab is no longer available. Mechanism of Action A member of the integrin family of adhe sion receptors, Gp IIb/IIIa is found on the surface of platelets and megakaryocytes. With about 80,000 copies per platelet, Gp IIb/IIIa is the most abundant receptor. Consisting of a noncovalently linked heterodimer, Gp IIb/IIIa is inactive on resting platelets. When platelets are activated, inside-outside signal transduction pathways trigger a conformational activation of the receptor. Once activated, Gp IIb/IIIa binds adhesive molecules, such as fibrinogen and, under high shear conditions, VWF. Binding is mediated by the Arg-Gly-Asp (RGD) sequence found on the α chains of fibrinogen and on VWF, and by the Lys-Gly-Asp (KGD) sequence located within a unique dodecapeptide domain on the γ chains of fibrinogen. Once bound, fibrinogen and/ or VWF bridge adjacent platelets together to induce platelet aggrega tion. Although abciximab, eptifibatide, and tirofiban all target the Gp IIb/IIIa receptor, they are structurally and pharmacologically distinct

(Table 123-1). Abciximab is a Fab fragment of a humanized murine

Reuptake Adenosine X Dipyridamole A2 Receptor Adenylate cyclase ATP Phosphodiesterase X AMP cAMP Ca2+ Activation and aggregation inhibited CHAPTER 123 monoclonal antibody directed against the activated form of Gp IIb/IIIa. Abciximab binds to the activated receptor with high affinity and blocks the binding of adhesive molecules. In contrast, eptifibatide and tirofiban are synthetic small molecules. Eptifibatide is a cyclic heptapeptide that binds Gp IIb/IIIa because it incorporates the KGD motif, whereas tiro fiban is a nonpeptidic tyrosine derivative that acts as an RGD mimetic. Abciximab has a long half-life and can be detected on the surface of platelets for up to 2 weeks; eptifibatide and tirofiban have short half-lives. Antiplatelet, Anticoagulant, and Fibrinolytic Drugs Indications Abciximab and eptifibatide are used in patients under going PCIs, particularly those who have not been pretreated with an ADP receptor antagonist. Tirofiban and eptifibatide are used in highrisk patients with non-ST-segment elevation MI. Dosing All the Gp IIb/IIIa antagonists are given as an IV bolus fol lowed by an infusion. The recommended dose of abciximab is a bolus of 0.25 mg/kg followed by an infusion of 0.125 µg/kg per minute to a maximum of 10 µg/kg for 12 h. In patients undergoing PCI, eptifiba tide is given as two 180 µg/kg boluses given 10 min apart, followed by an infusion of 2.0 µg/kg per minute for 18–24 h. For patients with acute coronary syndrome, the second eptifibatide bolus is withheld. Tirofi ban is started at a rate of 0.4 µg/kg per minute for 30 min; the drug is then continued at a rate of 0.1 µg/kg per minute for up to 18 h. Because eptifibatide and tirofiban are cleared by the kidneys, the doses must be reduced in patients with renal insufficiency. Thus, the eptifibatide infusion is reduced to 1 µg/kg per minute in patients with a creatinine clearance below 50 mL/min, whereas the dose of tirofiban is cut in half for patients with a creatinine clearance below 30 mL/min. TABLE 123-1 Features of Gp IIb/IIIa Antagonists FEATURE ABCIXIMAB EPTIFIBATIDE TIROFIBAN Description Fab fragment of humanized mouse monoclonal antibody Cyclical KGDcontaining heptapeptide Nonpeptidic RGD mimetic Specific for Gp IIb/IIIa No Yes Yes Plasma half-life Short (min) Long (2.5 h) Long (2.0 h) Platelet-bound half-life Long (days) Short (s) Short (s) Renal clearance No Yes Yes Abbreviation: Gp, glycoprotein.

Side Effects In addition to bleeding, thrombocytopenia is the most serious complication. Thrombocytopenia is immune-mediated and is caused by antibodies directed against neoantigens on Gp IIb/IIIa that are exposed upon antagonist binding. With abciximab, thrombocyto penia occurs in up to 5% of patients. Thrombocytopenia is severe in ~1% of these individuals. Thrombocytopenia is less common with the other two agents, occurring in ~1% of patients.

■ ■VORAPAXAR An orally active PAR-1 antagonist, vorapaxar blocks thrombin-induced platelet activation. Vorapaxar has a half-life of about 200 h. Indications When compared with a placebo in 12,944 patients with acute coronary syndrome without ST-segment elevation, vorapaxar failed to significantly reduce the primary efficacy endpoint, a compos ite of cardiovascular death, MI, stroke, recurrent ischemia requiring rehospitalization, and urgent coronary revascularization. Moreover, vorapaxar was associated with increased rates of bleeding, including intracranial bleeding. In a second trial, vorapaxar was compared with placebo for secondary prevention in 26,449 patients with prior MI, ischemic stroke, or peripheral arterial disease. Overall, vorapaxar reduced the risk of cardiovascular death, MI, or stroke by 13%, but doubled the risk of intracranial bleeding. In the prespecified subgroup of 17,779 patients with prior MI, however, vorapaxar reduced the risk for cardiovascular death, MI, or stroke by 20% compared with placebo (from 9.7% to 8.1%, respectively). The rate of intracranial hemorrhage was higher with vorapaxar than with placebo (0.6% and 0.4%, respectively;

p = .076) as was the rate of moderate or severe bleeding (3.4% and 2.1%, respectively; p <.0001). Based on these data, vorapaxar is licensed for patients younger than 75 years of age with MI or peripheral artery disease who have no history of stroke, transient ischemic attack, or intracranial bleeding and weigh >60 kg. PART 4 Oncology and Hematology Factor Xa A Unfractionated heparin Antithrombin Dosing Vorapaxar is given at a dose of 2.08 mg once daily. Side Effects The major side effect is bleeding. Platelet transfusion may be of ben efit for vorapaxar reversal. Low-molecularweight heparin B ANTICOAGULANTS There are both parenteral and oral anticoag ulants. The parenteral anticoagulants include heparin, low-molecular-weight heparin (LMWH), fondaparinux (a synthetic penta saccharide), lepirudin, desirudin, bivaliru din, and argatroban. Currently available oral anticoagulants include warfarin; dabigatran etexilate, an oral thrombin inhibitor; and rivaroxaban, apixaban, and edoxaban, which are oral factor Xa inhibitors. Pentasaccharide C ■ ■PARENTERAL ANTICOAGULANTS Heparin A sulfated polysaccharide, heparin is isolated from mammalian tis sues rich in mast cells. Most commercial heparin is derived from porcine intestinal mucosa and is a polymer of alternating

d-glucuronic acid and N-acetyl-d-glucos amine residues. FIGURE 123-5 Mechanism of action of heparin, low-molecular-weight heparin (LMWH), and fondaparinux, a synthetic pentasaccharide. A. Heparin binds to antithrombin via its pentasaccharide sequence. This induces a conformational change in the reactive center loop of antithrombin that accelerates its interaction with factor Xa. To potentiate thrombin inhibition, heparin must simultaneously bind to antithrombin and thrombin. Only heparin chains composed of at least 18 saccharide units, which corresponds to a molecular weight of 5400, are of sufficient length to perform this bridging function. With a mean molecular weight of 15,000, all the heparin chains are long enough to do this. B. LMWH has greater capacity to potentiate factor Xa inhibition by antithrombin than thrombin because, with a mean molecular weight of 4500–5000, at least half of the LMWH chains are too short to bridge antithrombin to thrombin. C. Fondaparinux, a synthetic pentasaccharide, only accelerates factor Xa inhibition by antithrombin because it is too short to bridge antithrombin to thrombin. MECHANISM OF ACTION Heparin acts as an anticoagulant by activating antithrombin

(previously known as antithrombin III) and accelerating the rate at which antithrombin inhibits clotting enzymes, particularly thrombin and factor Xa. Antithrombin, the obligatory plasma cofactor for hepa rin, is a member of the serine protease inhibitor (serpin) superfamily. Synthesized in the liver and circulating in plasma at a concentration of 2.6 ± 0.4 μM, antithrombin acts as a suicide substrate for its target enzymes. To activate antithrombin, heparin binds to the serpin via a unique pentasaccharide sequence that is found on one-third of the chains of commercial heparin (Fig. 123-5). Heparin chains without this pen tasaccharide sequence have little or no anticoagulant activity. Once bound to antithrombin, heparin induces a conformational change in the reactive center loop of antithrombin that renders it more readily accessible to its target proteases. This conformational change enhances the rate at which antithrombin inhibits factor Xa by at least two orders of magnitude but has little effect on the rate of thrombin inhibition. To catalyze thrombin inhibition, heparin serves as a template that binds antithrombin and thrombin simultaneously. Formation of this ternary complex brings the enzyme in close apposition to the inhibitor, thereby promoting the formation of a stable covalent thrombin-antithrombin complex. Only pentasaccharide-containing heparin chains composed of at least 18 saccharide units (which correspond to a molecular weight of 5400) are of sufficient length to bridge thrombin and antithrombin Pentasaccharide sequence Thrombin

together. With a mean molecular weight of 15,000, and a range of 5000–30,000, almost all the chains of unfractionated heparin are long enough to do so. Consequently, by definition, heparin has equal capac ity to promote the inhibition of thrombin and factor Xa by antithrom bin and is assigned an anti–factor Xa to anti–factor IIa (thrombin) ratio of 1:1. Heparin causes the release of tissue factor pathway inhibitor (TFPI) from the endothelium. A factor Xa–dependent inhibitor of tissue factor– bound factor VIIa, TFPI may contribute to the antithrombotic activity of heparin. Longer heparin chains induce the release of more TFPI than shorter ones. PHARMACOLOGY Heparin must be given parenterally. It is usu ally administered SC or by continuous IV infusion. When used for therapeutic purposes, the IV route is most often employed. If heparin is given SC for treatment of thrombosis, the dose of heparin must be high enough to overcome the limited bioavailability associated with this method of delivery. In the circulation, heparin binds to the endothelium and to plasma proteins other than antithrombin. Heparin binding to endothelial cells explains its dose-dependent clearance. At low doses, the halflife of heparin is short because it binds rapidly to the endothelium. With higher doses of heparin, the half-life is longer because heparin is cleared more slowly once the endothelium is saturated. Clearance is mainly extrarenal; heparin binds to macrophages, which internalize and depolymerize the long heparin chains and secrete shorter chains back into the circulation. Because of its dose-dependent clearance mechanism, the plasma half-life of heparin ranges from 30 to 60 min with bolus IV doses of 25 and 100 units/kg, respectively. Once heparin enters the circulation, it binds to plasma proteins other than antithrombin, a phenomenon that reduces its anticoagulant activity. Some of the heparin-binding proteins found in plasma are acute-phase reactants whose levels are elevated in ill patients. Others, such as high-molecular-weight multimers of VWF, are released from activated platelets or endothelial cells. Activated platelets also release platelet factor 4 (PF4), a highly cationic protein that binds heparin with high affinity. The large amounts of PF4 found in the vicinity of platelet-rich arterial thrombi can neutralize the anticoagulant activity of heparin. This phenomenon may attenuate heparin’s capacity to sup press thrombus growth. Because the levels of heparin-binding proteins in plasma vary from person to person, the anticoagulant response to fixed or weightadjusted doses of heparin is unpredictable. Consequently, coagula tion monitoring is essential to ensure that a therapeutic response is obtained. This is particularly important when heparin is administered for treatment of established thrombosis because a subtherapeutic anti coagulant response may render patients at risk for recurrent thrombo sis, whereas excessive anticoagulation increases the risk of bleeding. MONITORING THE ANTICOAGULANT EFFECT Heparin therapy can be monitored using the activated partial thromboplastin time (aPTT) or anti–factor Xa level. Although the aPTT is the test most often used for this purpose, there are problems with this assay. aPTT reagents vary in their sensitivity to heparin, and the type of coagulometer used for testing can influence the results. Consequently, laboratories must establish a therapeutic aPTT range with each reagent-coagulometer combination by measuring the aPTT and anti–factor Xa level in plasma samples collected from heparin-treated patients. For most of the aPTT reagents and coagulometers in current use, therapeutic heparin levels are achieved with a two- to threefold prolongation of the aPTT. Anti– factor Xa levels also can be used to monitor heparin therapy. With this test, therapeutic heparin levels range from 0.3 to 0.7 units/mL. Up to 25% of heparin-treated patients with VTE require

> 35,000 units/d to achieve a therapeutic aPTT. These patients are considered heparin resistant. It is useful to measure anti–factor Xa lev els in heparin-resistant patients because many will have a therapeutic anti–factor Xa level despite a subtherapeutic aPTT. This dissociation in test results occurs because elevated plasma levels of fibrinogen and factor VIII, both of which are acute-phase proteins, shorten the aPTT but have no effect on anti–factor Xa levels. Heparin therapy in patients

who exhibit this phenomenon is best monitored using anti–factor Xa levels instead of the aPTT. Patients with congenital or acquired anti thrombin deficiency and those with elevated levels of heparin-binding proteins may also need high doses of heparin to achieve a therapeutic aPTT or anti–factor Xa level. If there is good correlation between the aPTT and the anti–factor Xa level, either test can be used to monitor heparin therapy.

DOSING For prophylaxis, heparin is usually given in fixed doses of 5000 units SC two or three times daily. With these low doses, coagula tion monitoring is unnecessary. In contrast, monitoring is essential when the drug is given in therapeutic doses. Fixed-dose or weightbased heparin nomograms are used to standardize heparin dosing and to shorten the time required to achieve a therapeutic anticoagulant response. At least two heparin nomograms have been validated in patients with VTE and reduce the time required to achieve a thera peutic aPTT. Weight-adjusted heparin nomograms have also been evaluated in patients with acute coronary syndromes. After an IV heparin bolus of 5000 units or 70 units/kg, a heparin infusion rate of 12–15 units/kg per hour is usually administered. In contrast, weightadjusted heparin nomograms for patients with VTE use an initial bolus of 5000 units or 80 units/kg, followed by an infusion of 18 units/ kg per hour. Thus, patients with VTE appear to require higher doses of heparin to achieve a therapeutic aPTT than do patients with acute coronary syndromes. This may reflect differences in the thrombus bur den. Heparin binds to fibrin, and the amount of fibrin in patients with extensive DVT is greater than that in those with coronary thrombosis. CHAPTER 123 LIMITATIONS Heparin has pharmacokinetic and biophysical limitations (Table 123-2). The pharmacokinetic limitations reflect heparin’s propen sity to bind in a pentasaccharide-independent fashion to cells and plasma proteins. Heparin binding to endothelial cells explains its dose-dependent clearance, whereas binding to plasma proteins results in a variable antico agulant response and can lead to heparin resistance. Antiplatelet, Anticoagulant, and Fibrinolytic Drugs

The biophysical limitations of heparin reflect the inability of the heparin-antithrombin complex to inhibit factor Xa when it is incor porated into the prothrombinase complex, the complex that converts prothrombin to thrombin, and to inhibit thrombin bound to fibrin. Consequently, factor Xa bound to activated platelets within plateletrich thrombi has the potential to generate thrombin, even in the face of heparin. Once this thrombin binds to fibrin, it too is protected from inhibition by the heparin-antithrombin complex. Clot-associated thrombin can then trigger thrombus growth by locally activating platelets and amplifying its own generation through feedback activa tion of factors V, VIII, and XI. Further compounding the problem is the potential for heparin neutralization by the high concentrations of PF4 released from activated platelets within the platelet-rich thrombus. SIDE EFFECTS The most common side effect of heparin is bleeding. Other complications include thrombocytopenia, osteoporosis, and elevated levels of transaminases. Bleeding The risk of

bleeding rises as the dose of heparin is increased. Concomitant administration of drugs that affect hemostasis, such as antiplatelet or fibrinolytic agents, increases the risk of bleeding, as does TABLE 123-2 Pharmacokinetic and Biophysical Limitations of Heparin LIMITATIONS MECHANISM Poor bioavailability at low doses Binds to endothelial cells and macrophages Dose-dependent clearance Binds to macrophages Variable anticoagulant response Binds to plasma proteins whose levels vary from patient to patient Reduced activity in the vicinity of platelet-rich thrombi Neutralized by platelet factor 4 released from activated platelets Limited activity against factor Xa incorporated in the prothrombinase complex and thrombin bound to fibrin Reduced capacity of heparinantithrombin complex to inhibit factor Xa bound to activated platelets and thrombin bound to fibrin

TABLE 123-3 Features of Heparin-Induced Thrombocytopenia FEATURES DETAILS Thrombocytopenia Platelet count of ≤100,000/μL or a decrease in platelet count of ≥50% Timing Platelet count falls 5–14 days after starting heparin Type of heparin More common with unfractionated heparin than lowmolecular-weight heparin Type of patient More common in surgical patients and patients with cancer than general medical patients; more common in women than in men Thrombosis Venous thrombosis more common than arterial thrombosis recent surgery or trauma. Heparin-treated patients with serious bleed ing can be given protamine sulfate to neutralize the heparin. Protamine sulfate, a mixture of basic polypeptides isolated from salmon sperm, binds heparin with high affinity, and the resultant protamine-heparin complexes are then cleared. Typically, 1 mg of protamine sulfate neu tralizes 100 units of heparin. Protamine sulfate is given IV at a maxi mum amount of 50 mg per dose. Anaphylactoid reactions to protamine sulfate can occur, and drug administration by slow IV infusion is rec ommended to reduce the risk. Thrombocytopenia Heparin can cause thrombocytopenia. Heparininduced thrombocytopenia (HIT) is an antibody-mediated process that is triggered by antibodies directed against neoantigens on PF4 that are exposed when heparin binds to this protein. These antibod ies, which are usually of the IgG isotype, bind simultaneously to the heparin-PF4 complex and to platelet Fc receptors. Such binding acti vates the platelets and generates platelet microparticles. Circulating microparticles are procoagulant because they express anionic phos pholipids on their surface and can bind clotting factors and promote thrombin generation. The clinical features of HIT are illustrated in Table 123-3. Typically, HIT occurs 5–14 days after initiation of heparin therapy, but it can manifest earlier if the patient has received heparin within the past 3 months. A platelet count <100,000/μL or a 50% decrease in the platelet count from the pretreatment value should raise the suspicion of HIT. HIT is more common in surgical patients than in medical patients and, like many autoimmune disorders, occurs more frequently in females than in males. PART 4 Oncology and Hematology HIT can be associated with thrombosis, either arterial or venous. Venous thrombosis, which manifests as DVT and/or PE, is more com mon than arterial thrombosis. Arterial thrombosis can manifest as ischemic stroke or acute MI. Rarely, platelet-rich thrombi in the distal aorta or iliac arteries can cause critical limb ischemia. The diagnosis of HIT is established using enzyme-linked assays to detect antibodies against heparin-PF4 complexes or with platelet activation assays. Enzyme-linked assays are sensitive but can be posi tive in the absence of any clinical evidence of HIT. The most specific diagnostic test for HIT is the serotonin release assay. This test is per formed by quantifying serotonin release when washed platelets loaded with labeled serotonin are exposed to patient serum in the absence or presence of varying concentrations of heparin. If the patient serum contains the HIT antibody, heparin addition induces platelet activa tion and serotonin release. Management of HIT is outlined in Table 123-4. Heparin should be stopped in patients with

suspected or docu mented HIT, and an alternative anticoagulant should be administered TABLE 123-4 Management of Heparin-Induced Thrombocytopenia Stop all heparins. Give an alternative anticoagulant, such as argatroban, bivalirudin, fondaparinux, or rivaroxaban. Do not give platelet transfusions. Do not give warfarin until the platelet count returns to its baseline level. If warfarin was administered, give vitamin K to restore the INR to normal. Evaluate for thrombosis, particularly deep vein thrombosis. Abbreviation: INR, international normalized ratio.

to prevent or treat thrombosis. The agents most often used for this indication are parenteral direct thrombin inhibitors, such as argatroban or bivalirudin, or factor Xa inhibitors, such as fondaparinux or rivar oxaban. A HIT-like syndrome known as vaccine-induced thrombotic thrombocytopenia was reported as a rare complication after vaccina tion with adenovirus COVID-19 vaccines. Characterized by thrombo sis and thrombocytopenia that occurred 4–28 days after vaccination, patients presented with cerebral or splanchnic vein thrombosis as well as DVT or PE. The diagnosis is established by the detection of antibod ies against PF4 and a positive serotonin release assay with added PF4. Treatment can include intravenous immunoglobulin, steroids, and plasma exchange to offset the effects of the antibodies against PF4, as well as anticoagulants such as argatroban, fondaparinux, or rivaroxa ban to treat the thrombosis. Patients with HIT, particularly those with associated thrombosis, often have evidence of increased thrombin generation that can lead to consumption of protein C. If these patients are given warfarin without a concomitant anticoagulant that inhibits thrombin or thrombin genera tion, the further decrease in protein C levels induced by the warfarin can trigger skin necrosis. To avoid this problem, patients with HIT should be treated with a direct thrombin inhibitor or with fondaparinux until the platelet count returns to normal levels. At this point, low-dose warfarin therapy can be introduced, and the parenteral anticoagulant can be discontinued when the international normalized ratio (INR) has been therapeutic for at least 2 days. Alternatively, a direct oral antico agulant, such as apixaban or rivaroxaban, can be given. Osteoporosis Treatment with therapeutic doses of heparin for

> 1 month can cause a reduction in bone density. This complication has been reported in up to 30% of patients given long-term heparin therapy, and symptomatic vertebral fractures occur in 2–3% of these individuals. Heparin affects the activity of osteoblasts and osteoclasts and causes bone loss both by decreasing bone formation and by enhancing bone resorption. Elevated Levels of Transaminases Therapeutic doses of heparin are fre quently associated with modest elevations in the serum levels of hepatic transaminases without a concomitant increase in the level of bilirubin. The levels of transaminases rapidly return to normal when heparin is stopped. The mechanism responsible for this phenomenon is unknown. Low-Molecular-Weight Heparin Consisting of smaller frag ments of heparin, LMWH is prepared from unfractionated heparin by controlled enzymatic or chemical depolymerization. The mean molec ular weight of LMWH is about 5000, one-third the mean molecular weight of unfractionated heparin. LMWH has advantages over heparin (Table 123-5) and has replaced heparin for most indications. MECHANISM OF ACTION Like heparin, LMWH exerts its anticoagu lant activity by activating antithrombin. With a mean molecular weight of 5000, which corresponds to about 17 saccharide units, at least half of

> the pentasaccharide-containing chains of LMWH are too short to bridge thrombin to antithrombin (Fig. 123-5). However, these chains retain the capacity to accelerate factor Xa inhibition by antithrombin TABLE 123-5 Advantages of LMWH Over Heparin ADVANTAGE CONSEQUENCE Better bioavailability and longer halflife after subcutaneous injection Can be given subcutaneously once or twice daily for both prophylaxis and treatment Dose-independent clearance Simplified dosing Predictable anticoagulant response Coagulation monitoring is unnecessary in most patients Lower risk of heparin-induced thrombocytopenia Safer than heparin for short- or longterm administration Lower risk of osteoporosis Safer than heparin for extended administration Abbreviation: LMWH, low-molecular-weight heparin.

because this activity is largely the result of the conformational changes in antithrombin evoked by pentasaccharide binding. Consequently, LMWH catalyzes factor Xa inhibition by antithrombin more than thrombin inhibition. Depending on their unique molecular weight distributions, LMWH preparations have anti–factor Xa to anti–factor IIa ratios ranging from 2:1 to 4:1. PHARMACOLOGY Although usually given SC, LMWH also can be administered IV if a rapid anticoagulant response is needed. LMWH has pharmacokinetic advantages over heparin. These advantages reflect the fact that shorter heparin chains bind less avidly to endothe lial cells, macrophages, and heparin-binding plasma proteins. Reduced binding to endothelial cells and macrophages eliminates the rapid, dose-dependent, and saturable mechanism of clearance that is a char acteristic of unfractionated heparin. Instead, the clearance of LMWH is dose-independent and its plasma half-life is longer. Based on measure ment of anti–factor Xa levels, LMWH has a plasma half-life of ~4–6 h. LMWH is cleared almost exclusively by the kidneys, and the drug can accumulate in patients with renal insufficiency. LMWH exhibits about 90% bioavailability after SC injection. Because LMWH binds less avidly to heparin-binding proteins in plasma than heparin, LMWH produces a more predictable dose response, and resistance to LMWH is rare. With a longer half-life and more predictable anticoagulant response, LMWH can be given SC once or twice daily without coagulation monitoring, even when the drug is given in treatment doses. These properties render LMWH more convenient to administer than unfractionated heparin. Capitalizing on this feature, studies in patients with VTE have shown that home treatment with LMWH is as effective and safe as in-hospital treat ment with continuous IV infusions of heparin. Outpatient treatment with LMWH streamlines care, reduces health care costs, and increases patient satisfaction. MONITORING In most patients, LMWH does not require coagulation monitoring. If monitoring is necessary, anti–factor Xa levels must be measured because LMWH preparations have little effect on the aPTT. Therapeutic anti–factor Xa levels for once-daily and twice-daily dos ing of LMWH range from 0.5 to 1.2 units/mL and 1.0 to 2.0 units/mL, respectively, when measured 3–4 h after drug administration. When LMWH is given in prophylactic doses, peak anti–factor Xa levels of 0.2–0.5 units/mL are desirable. Indications for LMWH monitoring include renal impairment and obesity. LMWH monitoring in patients with a creatinine clearance ≤30 mL/min is advisable to ensure that there is no drug accumula tion. Although weight-adjusted LMWH dosing appears to produce therapeutic anti–factor Xa levels in patients who are overweight, this approach has not been extensively evaluated in those with morbid obe sity. It may also be advisable to monitor the anticoagulant activity of LMWH during pregnancy because dose requirements can change, par ticularly in the third trimester. Monitoring

should also be considered in high-risk settings, such as in pregnant women with mechanical heart valves who are given LMWH to prevent valve thrombosis, and when LMWH is used in treatment doses in infants or children. DOSING The doses of LMWH recommended for prophylaxis or treat ment vary depending on the LMWH preparation. For prophylaxis, once-daily SC doses of 4000–5000 units are often used, whereas doses of 2500–3000 units are given when the drug is administered twice daily. For treatment of VTE, a dose of 150–200 units/kg is given if the drug is administered once daily. If a twice-daily regimen is used, a dose of 100 units/kg is given. In patients with unstable angina, LMWH is given SC on a twice-daily basis at a dose of 100–120 units/kg. SIDE EFFECTS The major complication of LMWH is bleeding. Metaanalyses suggest that the risk of major bleeding is lower with LMWH than with unfractionated heparin. HIT and osteoporosis are less com mon with LMWH than with unfractionated heparin. Bleeding Like the situation with heparin, bleeding with LMWH is more common in patients receiving concomitant therapy with anti platelet or fibrinolytic drugs. Recent surgery, trauma, or underlying hemostatic defects also increase the risk of bleeding with LMWH.

Although protamine sulfate can be used as an antidote for LMWH, protamine sulfate incompletely neutralizes the anticoagulant activity of LMWH because it only binds the longer chains of LMWH. Because longer chains are responsible for catalysis of thrombin inhibition by antithrombin, protamine sulfate completely reverses the anti–factor IIa activity of LMWH. In contrast, protamine sulfate only partially reverses the anti–factor Xa activity of LMWH because the shorter pen tasaccharide-containing chains of LMWH do not bind to protamine sulfate. Consequently, patients at high risk for bleeding may be more safely treated with continuous IV unfractionated heparin than with SC LMWH. Andexanet alfa, a recombinant factor Xa variant licensed for reversal of oral factor Xa inhibitors, reverses that anti–factor Xa activity of LMWH but not its anti–factor IIa activity. The utility of andexanet for LMWH reversal is uncertain, and it is not licensed for this indication.

Thrombocytopenia The risk of HIT is about fivefold lower with LMWH than with heparin. LMWH binds less avidly to platelets and causes less PF4 release. Furthermore, with lower affinity for PF4 than heparin, LMWH is less likely to induce the conformational changes in PF4 that trigger the formation of HIT antibodies. LMWH should not be used to treat HIT patients because most HIT antibodies exhibit cross-reactivity with LMWH. This in vitro cross-reactivity is more than a laboratory phenomenon because there are case reports of thrombosis when HIT patients were switched from heparin to LMWH. CHAPTER 123 Osteoporosis Because the risk of osteoporosis is lower with LMWH than with heparin, LMWH is a better choice than heparin for extended treatment.
Antiplatelet, Anticoagulant, and Fibrinolytic Drugs
Fondaparinux A synthetic analogue of the antithrombin-binding pentasaccharide sequence, fondaparinux differs from LMWH in sev eral ways (Table 123-6). Fondaparinux is licensed for thromboprophy laxis in general medical or surgical patients and in high-risk orthopedic patients and as an alternative to heparin or LMWH for initial treatment of patients with established VTE. Although fondaparinux is used in Europe as an alternative to heparin or LMWH in patients with acute coronary syndrome, the drug is not licensed for this indication in the United States. MECHANISM OF ACTION Fondaparinux has a molecular weight of 1728. Fondaparinux binds only to antithrombin (Fig. 123-5) and is too short to bridge thrombin to antithrombin. Consequently, fondaparinux catalyzes factor Xa inhibition by antithrombin and does not enhance the rate of thrombin inhibition. PHARMACOLOGY Fondaparinux exhibits complete bioavailability after SC injection. With no binding to endothelial cells or plasma proteins, the clearance of fondaparinux is

dose independent, and its plasma half-life is 17 h. The drug is given SC once daily. Because fondaparinux is cleared unchanged via the kidneys, it is contraindi cated in patients with a creatinine clearance <30 mL/min and should be used with caution in those with a creatinine clearance <50 mL/min. DOSING Fondaparinux produces a predictable anticoagulant response after administration in fixed doses because it does not bind to plasma proteins. The drug is given at a dose of 2.5 mg once daily for preven tion of VTE. For initial treatment of established VTE, fondaparinux is TABLE 123-6 Comparison of LMWH and Fondaparinux FEATURES LMWH FONDAPARINUX Number of saccharide units 15–17

Catalysis of factor Xa inhibition Yes Yes Catalysis of thrombin inhibition Yes No Bioavailability after subcutaneous administration (%)

Plasma half-life (h)

Renal excretion Yes Yes Induces release of tissue factor pathway inhibitor Yes No Neutralized by protamine sulfate Partially No

given at a dose of 7.5 mg once daily. The dose can be reduced to 5 mg once daily for those weighing <50 kg and increased to 10 mg for those

> 100 kg. When given in these doses, fondaparinux is as effective as heparin or LMWH for initial treatment of patients with DVT or PE and is associated with similar rates of bleeding.

Fondaparinux is used at a dose of 2.5 mg once daily in patients with acute coronary syndrome. When this prophylactic dose of fondaparinux was compared with treatment doses of enoxaparin in patients with non-ST-segment elevation MI, there was no difference in the rate of cardiovascular death, MI, or stroke at 9 days. However, the rate of major bleeding was 50% lower with fondaparinux than with enoxaparin, a difference that likely reflects the fact that the dose of fondaparinux was lower than that of enoxaparin. In acute coronary syndrome patients who require PCI, there is a risk of catheter throm bosis with fondaparinux unless adjunctive heparin is given at the time of the procedure. SIDE EFFECTS Fondaparinux does not cause HIT because it does not bind to PF4. In contrast to LMWH, there is no cross-reactivity of fondaparinux with HIT antibodies. Consequently, fondaparinux appears to be effective for treatment of HIT patients, although large clinical trials supporting its use are lacking. The major side effect of fondaparinux is bleeding. Fondaparinux has no antidote. Protamine sulfate has no effect on the anticoagulant activity of fondaparinux because it fails to bind to the drug. Andexanet alfa has been reported to reverse fondaparinux in vitro, but studies in patients are lacking. Recombinant activated factor VII reverses the anticoagulant effects of fondaparinux in volunteers, but it is unknown whether this agent controls fondaparinux-induced bleeding. PART 4 Oncology and Hematology Parenteral Direct Thrombin Inhibitors Direct thrombin inhibi tors bind directly to thrombin and block its interaction with its substrates. Approved parenteral direct thrombin inhibitors include recombinant hirudins (lepirudin and desirudin), argatroban, and bivalirudin (Table 123-7). Lepirudin and desirudin are no longer available. ARGATROBAN A univalent inhibitor that targets the active site of thrombin,

argatroban is metabolized in the liver. Consequently, this drug must be used with caution in patients with hepatic insufficiency. Argatroban is administered by continuous IV infusion and has a plasma half-life of ~45 min. The aPTT is used to monitor its anticoagu lant effect, and the dose is adjusted to achieve an aPTT 1.5–3 times the baseline value, but not to exceed 100 s. Argatroban also prolongs the INR, a feature that can complicate the transitioning of patients from argatroban to warfarin. This problem can be circumvented by using the levels of factor X to monitor warfarin instead of the INR. Alternatively, argatroban can be stopped for 2–3 h before INR determination. Argatroban is licensed for treatment of patients with HIT or a his tory of HIT, including those requiring PCI. In such patients, argatroban is most useful for those with severe kidney disease because unlike fondaparinux and bivalirudin, it is not cleared through the kidneys. BIVALIRUDIN A synthetic 20-amino-acid analogue of hirudin, bivali rudin is a divalent thrombin inhibitor. Thus, the N-terminus of bivali rudin interacts with the active site of thrombin, whereas its C-terminus binds to exosite 1. Bivalirudin has a plasma half-life of 25 min, the shortest half-life of all the parenteral direct thrombin inhibitors. Bivalirudin is degraded by peptidases and is partially excreted via the TABLE 123-7 Comparison of the Properties of Desirudin, Bivalirudin, and Argatroban DESIRUDIN BIVALIRUDIN ARGATROBAN Molecular mass

Site(s) of interaction with thrombin Active site and exosite 1 Active site and exosite 1 Active site Renal clearance Yes No No Hepatic metabolism No No Yes Plasma half-life (min) 60 (IV) 120–180 (SC)

kidneys. When given in high doses in the cardiac catheterization labo ratory, the anticoagulant activity of bivalirudin is monitored using the activated clotting time. With lower doses, its activity can be assessed using the aPTT. Bivalirudin is licensed as an alternative to heparin in patients under going PCI. Bivalirudin also has been used successfully in HIT patients who require PCI or cardiac bypass surgery. ■ ■ORAL ANTICOAGULANTS For many years, vitamin K antagonists such as warfarin were the only available oral anticoagulants. This situation changed with the intro duction of the direct oral anticoagulants, which include dabigatran, rivaroxaban, apixaban, and edoxaban. Warfarin A water-soluble vitamin K antagonist initially developed as a rodenticide; warfarin is the coumarin derivative most often pre scribed in North America. Like other vitamin K antagonists, warfarin interferes with the synthesis of the vitamin K–dependent clotting pro teins, which include prothrombin (factor II) and factors VII, IX, and X. The synthesis of the vitamin K–dependent anticoagulant proteins, proteins C and S, is also reduced by vitamin K antagonists. MECHANISM OF ACTION All of the vitamin K–dependent clotting factors possess glutamic acid residues at their N termini. A posttransla tional modification adds a carboxyl group to the γ-carbon of these resi dues to generate γ-carboxyglutamic acid. This modification is essential for expression of the activity of these clotting factors because it permits their calcium-dependent binding to negatively charged phospholipid surfaces. The γ-carboxylation process is catalyzed by a vitamin K–dependent carboxylase. Thus, vitamin K from the diet is reduced to vitamin K hydroquinone by vitamin K reductase (Fig. 123-6). Vita min K hydroquinone serves as a cofactor for the carboxylase enzyme, which in the presence of carbon dioxide replaces the hydrogen on the γ-carbon of glutamic acid residues with a carboxyl group. During this process, vitamin K hydroquinone is oxidized to vitamin K epoxide, which is then reduced to vitamin K by vitamin K epoxide reductase. Nonfunctional Prozymogens Functional Zymogens γ-glutamyl carboxylase O2 CO2 Reduced vitamin K Vitamin K cycle Oxidized vitamin K Vitamin K reductase x CYP1A1 CYP1A2 CYP3A4 CYP2C9 R-warfarin S-warfarin Warfarin metabolism Warfarin FIGURE 123-6 Mechanism of action of warfarin. A

racemic mixture of S- and R-enantiomers, S-warfarin is most active. By blocking vitamin K epoxide reductase, warfarin inhibits the conversion of oxidized vitamin K into its reduced form. This inhibits vitamin K–dependent γ-carboxylation of factors II, VII, IX, and X because reduced vitamin K serves as a cofactor for a γ-glutamyl carboxylase that catalyzes the γ-carboxylation process, thereby converting pro-zymogens to zymogens capable of binding calcium and interacting with anionic phospholipid surfaces. S-warfarin is metabolized by CYP2C9. Common genetic polymorphisms in this enzyme can influence warfarin metabolism. Polymorphisms in the C1 subunit of vitamin K reductase (VKORC1) also can affect the susceptibility of the enzyme to warfarin-induced inhibition, thereby influencing warfarin dosage requirements.

Warfarin inhibits vitamin K epoxide reductase (VKOR), thereby blocking the γ-carboxylation process. This results in the synthesis of vitamin K–dependent clotting proteins that are only partially γ-carboxylated. Warfarin acts as an anticoagulant because these par tially γ-carboxylated proteins have little or no biological activity. The onset of action of warfarin is delayed until the newly synthesized clot ting factors with reduced activity gradually replace their fully active counterparts. The antithrombotic effect of warfarin depends on a reduction in the functional levels of factor X and prothrombin, clotting factors that have half-lives of 24 and 72 h, respectively. Because the antithrombotic effect of warfarin is delayed, patients with established thrombosis or at high risk for thrombosis require concomitant treatment with a rapidly acting parenteral anticoagulant, such as heparin, LMWH, or fondaparinux, for at least 5 days. PHARMACOLOGY Warfarin is a racemic mixture of R and S isomers. Warfarin is rapidly and almost completely absorbed from the gastroin testinal tract. Levels of warfarin in the blood peak about 90 min after drug administration. Racemic warfarin has a plasma half-life of 36–42 h, and >97% of circulating warfarin is bound to albumin. Only the small fraction of unbound warfarin is biologically active. Warfarin accumulates in the liver where the two isomers are metab olized via distinct pathways. CYP2C9 mediates oxidative metabolism of the more active S isomer (Fig. 123-6). Two relatively common variants, CYP2C9*2 and CYP2C9*3, encode an enzyme with reduced activity. Patients with these variants require lower maintenance doses of war farin. Approximately 25% of Caucasians have at least one variant allele of CYP2C9*2 or CYP2C9*3, whereas those variant alleles are less com mon in African Americans and Asians (Table 123-8). Heterozygosity for CYP2C9*2 or CYP2C9*3* decreases the warfarin dose requirement by 20–30% relative to that required in subjects with the wild-type CYP2C9*1/1 alleles, whereas homozygosity for the CYP2C92 or CYP2C9*3 alleles reduces the warfarin dose requirement by 50–70%. Consistent with their decreased warfarin dose requirement, subjects with at least one CYP2C9 variant allele are at increased risk for bleed ing. Compared with individuals with no variant alleles, the risk of warfarin-associated bleeding is almost twofold higher in CYP2C9*2 or CYP2C9*3 carriers. Polymorphisms in VKORC1 also can influence the anticoagulant response to warfarin. Several genetic variations of VKORC1 are in strong linkage disequilibrium and have been designated as non-A

haplotypes. VKORC1 variants are more prevalent than variants of CYP2C9. Asians have the highest prevalence of VKORC1 variants, followed by Caucasians and African Americans (Table 123-8). Poly morphisms in VKORC1 likely explain 30% of the variability in war farin dose requirements. Compared with VKORC1 non-A/non-A TABLE 123-8 Frequencies of CYP2C9 Genotypes and VKORC1 Haplotypes in Different Populations and their Effect on Warfarin Dose Requirements FREQUENCY, % PERCENTAGE DOSE REDUCTION COMPARED WITH WILD-TYPE CAUCASIANS AFRICAN AMERICANS (A/A) ASIANS (A) GENOTYPE/ HAPLOTYPE CYP2C9 *1/*1

— *1/*2

*1/*3

*2/*2

*2/*3

*3/*3

VKORC1 Non-A/non-A

— Non-A/A

A/A

homozygotes, the warfarin dose requirement decreases by 25 and 50% in A haplotype heterozygotes and homozygotes, respectively. These findings prompted the U.S. Food and Drug Administration (FDA) to amend the prescribing information for warfarin to indicate that lower initiation doses should be considered for patients with CYP2C9 and VKORC1 genetic variants. In addition to genotype data, other perti nent patient information has been incorporated into warfarin dosing algorithms. Although such algorithms help predict suitable warfarin doses, it remains unclear whether better dose identification improves patient outcome in terms of reducing hemorrhagic complications or recurrent thrombotic events.

In addition to genetic factors, the anticoagulant effect of warfarin is influenced by diet, drugs, and various disease states. Fluctuations in dietary vitamin K intake affect the activity of warfarin. A wide variety of drugs can alter absorption, clearance, or metabolism of warfarin. Because of the variability in the anticoagulant response to warfa rin, coagulation monitoring is essential to ensure that a therapeutic response is obtained. MONITORING Warfarin therapy is most often monitored using the prothrombin time, a test that is sensitive to reductions in the levels of prothrombin, factor VII, and factor X. The test is performed by adding thromboplastin, a reagent that contains tissue factor, phospholipid, and calcium, to citrated plasma and determining the time to clot formation. Thromboplastins vary in their sensitivity to reductions in the levels of the vitamin K–dependent clotting factors. Thus, less sensitive throm boplastins will trigger the administration of higher doses of warfarin to achieve a target prothrombin time. This is problematic because higher doses of warfarin increase the risk of bleeding. CHAPTER 123 Antiplatelet, Anticoagulant, and Fibrinolytic Drugs
The INR was developed to circumvent many of the problems asso ciated with the prothrombin time. To calculate the INR, the patient’s prothrombin time is divided by the mean normal prothrombin time, and this ratio is then multiplied by the international sensitivity index (ISI), which is an index of the sensitivity of the thromboplastin used for prothrombin time determination to reductions in the levels of the vitamin K–dependent clotting factors. Sensitive thromboplastins have an ISI near 1.0. Most current thromboplastins have ISI values that range from 0.9 to 1.4. Although the INR has helped to standardize anticoagulant practice, problems persist. The precision of INR determination varies depend ing on reagent-coagulometer combinations. This leads to variability in the INR results. Also complicating INR determination is unreliable reporting of the ISI by thromboplastin

manufacturers. Furthermore, every laboratory must establish the mean normal prothrombin time with each new batch of thromboplastin reagent. To accomplish this, the prothrombin time must be measured in fresh plasma samples from at least 20 healthy volunteers using the same coagulometer that is used for patient samples. For most indications, warfarin is administered in doses that produce a target INR of 2.0–3.0. An exception is patients with mechanical heart valves, particularly those in the mitral position or older ball and cage valves in the aortic position, and valves in any position associated with atrial fibrillation, where a target INR of 2.5–3.5 is recommended. Stud ies in atrial fibrillation demonstrate an increased risk of cardioembolic stroke when the INR falls below 1.7 and an increase in bleeding with INR values >4.5. These findings highlight the fact that vitamin K antag onists have a narrow therapeutic window. In support of this concept, a study in patients receiving long-term warfarin therapy for unprovoked VTE demonstrated a higher rate of recurrent VTE with a target INR of 1.5–1.9 compared with a target INR of 2.0–3.0. DOSING Warfarin is usually started at a dose of 5–10 mg. Lower doses are used for patients with CYP2C9 or VKORC1 polymorphisms, which affect the pharmacodynamics or pharmacokinetics of warfarin and render patients more sensitive to the drug. The dose is then titrated to achieve the desired target INR. Because of its delayed onset of action, patients with established thrombosis or those at high risk for throm bosis are given concomitant initial treatment with a rapidly acting parenteral anticoagulant, such as heparin, LMWH, or fondaparinux. Early prolongation of the INR reflects reduction in the functional levels

of factor VII. Consequently, concomitant treatment with the parenteral anticoagulant should be continued until the INR has been therapeutic for at least 2 consecutive days. A minimum 5-day course of parenteral anticoagulation is recommended to ensure that the levels of factor Xa and prothrombin have been reduced into the therapeutic range with warfarin.

Because warfarin has a narrow therapeutic window, frequent coagulation monitoring is essential to ensure that a therapeutic anti coagulant response is maintained. Even patients with stable warfarin dose requirements should have their INR determined every 3–4 weeks although there are studies suggesting that less frequent monitoring is feasible. More frequent monitoring is necessary when new medica tions are introduced because so many drugs enhance or reduce the anticoagulant effects of warfarin and when the dosing regimen has been changed. SIDE EFFECTS Like all anticoagulants, the major side effect of warfa rin is bleeding. A rare complication is skin necrosis. Warfarin crosses the placenta and can cause fetal abnormalities. Consequently, warfarin should not be used during pregnancy. Bleeding At least half of the bleeding complications with warfarin occur when the INR exceeds the therapeutic range. Bleeding compli cations may be mild, such as epistaxis or hematuria, or more severe, such as retroperitoneal or gastrointestinal bleeding. Life-threatening intracranial bleeding can also occur. PART 4 Oncology and Hematology To minimize the risk of bleeding, the INR should be maintained in the therapeutic range. In asymptomatic patients whose INR is between 3.5 and 10, warfarin should be withheld until the INR returns to the therapeutic range. If the INR is over 10, oral vitamin K can be admin istered at a dose of 2.5–5 mg, although there is no evidence that doing so reduces the bleeding risk. Higher doses of oral vitamin K (5–10 mg) produce more rapid reversal of the INR but may render patients tem porarily resistant to warfarin when the drug is restarted. Patients with an increased INR associated with serious bleeding should be given 5–10 mg of vitamin K by slow IV infusion. Addi tional vitamin K should be given until the INR is in the normal range. Treatment with vitamin K should be supplemented with four-factor prothrombin complex concentrate, which contains all four vitamin K– dependent clotting

proteins. Prothrombin complex concentrate nor malizes the INR more rapidly than transfusion of fresh-frozen plasma. Warfarin-treated patients who experience bleeding when their INR is in the therapeutic range require investigation into the cause of the bleeding. Those with gastrointestinal or genitourinary bleeding often have underlying disorders. Skin Necrosis A rare complication of warfarin, skin necrosis usually is seen 2–5 days after initiation of therapy. Well-demarcated erythema tous lesions form on the thighs, buttocks, breasts, or toes. Typically, the center of the lesion becomes progressively necrotic. Examination of skin biopsies taken from the border of these lesions reveals thrombi in the microvasculature. Warfarin-induced skin necrosis is seen in patients with congenital or acquired deficiencies of protein C or protein S. Initiation of warfarin therapy in these patients produces a precipitous fall in plasma levels of proteins C or S, thereby eliminating this important anticoagulant path way before warfarin exerts an antithrombotic effect through lowering of the functional levels of factor X and prothrombin. The resultant pro coagulant state triggers thrombosis. Why the thrombosis is localized to the microvasculature of fatty tissues is unclear. Treatment involves discontinuation of warfarin and reversal with vitamin K, if needed. An alternative anticoagulant, such as heparin or LMWH, should be given in patients with thrombosis. Protein C con centrate can be given to protein C–deficient patients to accelerate heal ing of the skin lesions; fresh-frozen plasma may be of value if protein C concentrate is unavailable and for those with protein S deficiency. Occasionally, skin grafting is necessary when there is extensive skin loss. Because of the potential for skin necrosis, patients with known protein C or protein S deficiency require overlapping treatment with a parenteral anticoagulant when initiating warfarin therapy. Warfarin

should be started in low doses in these patients, and the parenteral anticoagulant should be continued until the INR is therapeutic for at least 2–3 consecutive days. Alternatively, treatment with rivaroxaban or apixaban could be given, although there is limited information about their efficacy and safety in patients with severe protein C or S deficiency. Pregnancy Warfarin crosses the placenta and can cause fetal abnor malities or bleeding. The fetal abnormalities include a characteristic embryopathy, which consists of nasal hypoplasia and stippled epiphy ses. The risk of embryopathy is highest if warfarin is given in the first trimester of pregnancy. Central nervous system abnormalities can also occur with exposure to warfarin at any time during pregnancy. Finally, maternal administration of warfarin produces an anticoagulant effect in the fetus that can cause bleeding. This is of particular concern at delivery when trauma to the head during passage through the birth canal can lead to intracranial bleeding. Because of these potential prob lems, warfarin is contraindicated in pregnancy, particularly in the first and third trimesters. Instead, heparin, LMWH, or fondaparinux can be given during pregnancy for prevention or treatment of thrombosis. Warfarin does not pass into the breast milk. Consequently, warfarin can safely be given to nursing mothers. Special Problems Patients with antiphospholipid syndrome and those who need urgent or elective surgery present special challenges. Although observational studies suggested that patients with thrombo sis complicating antiphospholipid syndrome required higher intensity warfarin regimens to prevent recurrent thromboembolic events, two randomized trials showed that targeting an INR of 2.0–3.0 is as effec tive as higher intensity treatment and produces less bleeding. Moni toring warfarin therapy can be problematic in patients with the lupus anticoagulant because it prolongs the baseline INR; factor X levels can be used instead of the INR in such patients. There is no need to stop warfarin before procedures associated with a low risk of bleeding; these include dental cleaning, simple dental extraction, cataract surgery, or skin biopsy. For procedures associated with a moderate or high risk of bleeding, warfarin should be stopped 5

days before the procedure to allow the INR to return to normal lev els. Patients at high risk for thrombosis, such as those with mechanical heart valves, can be bridged with once- or twice-daily SC injections of LMWH when the INR falls to <2.0. The last dose of LMWH should be given 12–24 h before the procedure, depending on whether LMWH is administered twice or once daily. After the procedure, treatment with warfarin can be restarted. Direct Oral Anticoagulants The direct oral anticoagulants (DOACs) include dabigatran, which inhibits thrombin, and rivar oxaban, apixaban, and edoxaban, which inhibit factor Xa. These drugs have a rapid onset and offset of action and have half-lives that permit once- or twice-daily administration. Designed to produce a predictable level of anticoagulation, the DOACs are more convenient to administer than warfarin because they are given in fixed doses without routine coagulation monitoring. MECHANISM OF ACTION The DOACs are small molecules that bind reversibly to the active site of their target enzyme. Table 123-9 sum marizes the distinct pharmacologic properties of these agents. INDICATIONS All four DOACs are licensed for stroke prevention in patients with atrial fibrillation except those with mechanical heart valves or severe rheumatic mitral valve disease, and for treatment of VTE. Dabigatran, rivaroxaban, and apixaban are licensed for throm boprophylaxis after elective hip or knee arthroplasty; edoxaban is only licensed for this indication in Japan. Finally, low-dose rivaroxaban is licensed for use with aspirin for secondary prevention in patients with coronary or peripheral artery disease. DOSING For prevention of stroke in patients with atrial fibrillation, rivaroxaban is given at a dosage of 20 mg once daily, with a reduction to 15 mg once daily in patients with a creatinine clearance of 15–49 mL/ min; dabigatran is given at a dosage of 150 mg twice daily, with a reduction to 75 mg twice daily in those with a creatinine clearance of 15–30 mL/min; apixaban is given at a dosage of 5 mg twice daily, with a reduction to 2.5 mg twice daily for patients with at least two of the

TABLE 123-9 Comparison of the Pharmacologic Properties of the Direct Oral Anticoagulants CHARACTERISTIC RIVAROXABAN APIXABAN EDOXABAN DABIGATRAN Target Factor Xa Factor Xa Factor Xa Thrombin Prodrug No No No Yes Bioavailability 80% 60% 50% 6% Dosing qd (bid) bid qd bid (qd) Half-life 7–11 h 12 h 9–11 h 12–17 h Renal excretion 33% (66%) 25% 35% 80% Interactions 3A4/P-gp 3A4/P-gp P-gp P-gp Abbreviations: bid, twice a day; P-gp, P-glycoprotein; qd, once a day. “ABC” criteria (i.e., age >80 years, body weight <60 kg, and creatinine

> 1.5 g/dL); and edoxaban is given at a dosage of 60 mg once daily for patients with a creatinine clearance of 50–95 mL/min and with a reduction to 30 mg once daily for patients with any one of the follow ing criteria: creatinine clearance of 15–50 mL/min, body weight of

60 kg or less, or use of potent P-glycoprotein inhibitors, such as vera pamil or quinidine. At doses of 15 or 20 mg once daily, rivaroxaban must be administered with food to enhance absorption. Apixaban and edoxaban can be given with or without food. Administration of dabi gatran with food may reduce dyspepsia. For treatment of VTE, dabigatran and edoxaban are started after patients have received at least a 5-day course of treatment with a par enteral anticoagulant such as LMWH. Dabigatran is given at a dose of 150 mg twice daily provided the creatinine clearance is >30 mL/min. The dosage regimen for edoxaban is identical to that used in patients with atrial fibrillation. Rivaroxaban and apixaban can be given in alloral regimens; rivaroxaban is started at a

dose of 15 mg twice daily for 21 days and is then reduced to 20 mg once daily thereafter, whereas apixaban is started at a dose of 10 mg twice daily for 7 days and is then reduced to 5 mg twice daily thereafter. For secondary VTE prevention after 6 months of full-dose treatment, the dosage of apixaban can be lowered to 2.5 mg twice daily while the dose of rivaroxaban can be lowered to 10 mg once daily, doses that have safety profiles like those of placebo and aspirin, respectively. Thromboprophylaxis after elective hip or knee replacement surgery is started after surgery and is often continued for 30 days in patients undergoing hip replacement and for 10–14 days in patients undergo ing knee replacement. Dabigatran is given at a dose of 220 mg once daily, whereas rivaroxaban and apixaban are given at doses of 10 mg once daily and 2.5 mg twice daily, respectively. In lower risk patients undergoing hip or knee replacement surgery, a 5-day course of rivar oxaban followed by a 30-day course of aspirin at a dose of 81 mg daily appears to be as effective and safe as extended thromboprophylaxis with rivaroxaban. For secondary prevention of adverse cardiac or limb events in patients with coronary or peripheral artery disease, rivaroxaban is given at a dose of 2.5 mg twice daily on top of aspirin (81 or 100 mg once daily). MONITORING Although designed to be administered without routine monitoring, there are situations where determination of the anticoagu lant activity of the DOACs can be helpful. These include assessment of adherence, detection of accumulation or overdose, identification of bleeding mechanisms, and determination of activity before surgery, intervention, or reversal. For qualitative assessment of anticoagulant activity, the prothrombin time can be used for factor Xa inhibitors and the aPTT for dabigatran. Rivaroxaban and edoxaban prolong the prothrombin time more than apixaban. In fact, because apixaban has such a limited effect on the prothrombin time, anti–factor Xa assays are needed to assess its activity. The effect of the drugs on tests of coagula tion varies depending on the time that the blood is drawn relative to the timing of the last dose of the drug and the reagents used to perform the tests. Chromogenic anti–factor Xa assays and the diluted thrombin clotting time or ecarin clot time with appropriate calibrators provide quantitative assays to measure the plasma levels of the factor Xa inhibi tors and dabigatran, respectively.

SIDE EFFECTS Like all anticoagulants, bleeding is the most com mon side effect of the DOACs. The DOACS are associated with less intracranial bleeding than warfarin, but the higher dose regimens of dabigatran, rivaroxaban, and edoxaban are associated with more gas trointestinal bleeding. Dyspepsia occurs in up to 10% of patients treated with dabigatran; this problem improves with time and can be minimized by administer ing the drug with food. Dyspepsia is rare with rivaroxaban, apixaban, and edoxaban. CHAPTER 123 PERIPROCEDURAL MANAGEMENT Like warfarin, the DOACs must be stopped before procedures associated with a moderate or high risk of bleeding. The drugs should be held for 1–2 days, or longer if renal function is impaired. Assessment of residual anticoagulant activity before procedures associated with a high bleeding risk is prudent.

MANAGEMENT OF BLEEDING With minor bleeding, withholding one or two doses of drug is usually sufficient. With more serious bleeding, the approach is like that with warfarin, except that vitamin K adminis tration is of no benefit; the anticoagulant and any long-acting antiplate let drugs should be withheld, the patient should be resuscitated with fluids and blood products as necessary, and the bleeding site should be identified and managed. Coagulation testing or measurement of the DOAC level will determine the extent of anticoagulation, and renal function should be assessed so that the half-life of the drug can be calculated. Timing of the last dose of anticoagulant is important; in cases of overdose, oral activated charcoal may help prevent absorption of drug administered in the past 4 h. If >24 h have elapsed since the last intake, the DOAC is unlikely to be responsible for the

bleeding unless there is marked impairment of renal function. Anticoagulant reversal should be considered if bleeding continues despite supportive measures or if the bleeding is life-threatening or occurs in a critical organ (e.g., intracranial) or in a closed space (e.g., the pericardium or retroperitoneum). Idarucizumab is licensed for dabigatran reversal in such patients or in those requiring urgent sur gery or intervention. A humanized antibody fragment, idarucizumab, binds dabigatran with high affinity to form an essentially irreversible complex that is cleared by the kidneys. Idarucizumab is given intrave nously as a 5-g bolus and is supplied in a box containing two 50-mL vials, each containing 2.5 g of idarucizumab. Idarucizumab rapidly reverses the anticoagulant effects of dabigatran and normalizes the aPTT, diluted thrombin time, or ecarin clot time. Andexanet alfa is available for reversal of rivaroxaban and apixaban. A recombinant variant of factor Xa without catalytic activity, andexanet serves as a decoy to sequester oral factor Xa inhibitors until they are cleared from the circulation. Low- or high-dose IV andexanet regimens are used. The low-dose regimen starts with a bolus of 400 mg followed by an infusion of 4 mg/min for up to 120 min, whereas the high-dose regi men starts with a bolus of 800 mg followed by an infusion of 8 mg/min for up to 120 min. The low-dose regimen is used for reversal of doses of rivaroxaban or apixaban of 10 mg or 5 mg or less, respectively, or for any dose of rivaroxaban or apixaban if the last dose was taken >8 h before presentation. The high-dose regimen is used to reverse rivaroxa ban or apixaban doses over 10 and 5 mg, respectively, if the last dose was taken <8 h since presentation, or if the timing of the last dose of rivaroxaban or apixaban is unknown.

Andexanet alfa is expensive and is not available in all hospitals. Because of its cost, andexanet alfa is often reserved for reversal in patients with life-threatening bleeds such intracranial hemorrhage or bleeds into a closed space such as retroperitoneal or pericardial bleeds. If andexanet is unavailable, the results of prospective cohort studies suggest that four-factor prothrombin complex concentrate (25–50 units/kg) also is effective at restoring hemostasis. If there is continued bleeding, acti vated prothrombin complex concentrate (50 units/kg) or recombinant factor VIIa (90 µg/kg) can be considered.

Neither andexanet alfa nor four-factor prothrombin complex con centrate has been evaluated for reversal in patients requiring urgent surgery or intervention. Furthermore, andexanet alfa not only reverses oral factor Xa inhibitors but also reverses heparin and LMWH. This could be problematic in patients who require cardiac surgery or vas cular surgery, procedures where heparin is used routinely. To circum vent this problem, most surgical procedures and interventions can be undertaken without reversal, and four-factor prothrombin complex concentrate can be given if necessary. For patients requiring surgery to stop bleeding such as those with a ruptured aortic aneurysm or with bleeding secondary to polytrauma, upfront four-factor prothrombin concentrate administration can be considered. PREGNANCY As small molecules, the DOACs pass through the pla centa. Consequently, these agents are contraindicated in pregnancy, and when used by women of childbearing potential, appropriate con traception is important. DOACs should be avoided in nursing mothers because small amounts have been found in breast milk. PART 4 Oncology and Hematology FIBRINOLYTIC DRUGS ■ ■ROLE OF FIBRINOLYTIC THERAPY Fibrinolytic drugs are used to degrade thrombi and are administered systemically or can be delivered via catheters directly into the substance of the thrombus. Systemic delivery is used for treatment of acute MI, acute ischemic stroke, and most cases of massive PE. The goal of ther apy is to produce rapid thrombus dissolution, thereby restoring blood flow. In the coronary circulation, restoration of blood flow reduces morbidity and mortality rates by limiting myocardial damage, whereas in the cerebral

circulation, rapid thrombus dissolution decreases the neuronal death and brain infarction that produce irreversible brain injury. For patients with massive PE, the goal of thrombolytic therapy is to restore pulmonary artery perfusion. Peripheral arterial thrombi and thrombi in the proximal deep veins of the leg are most often treated using catheter-directed thrombolytic therapy. Catheters with multiple side holes can be used to enhance drug delivery. In some cases, intravascular devices that fragment and extract the thrombus are used to hasten treatment. These devices can be used alone or in conjunction with fibrinolytic drugs. ■ ■MECHANISM OF ACTION Currently approved fibrinolytic agents include streptokinase; acylated plasminogen streptokinase activator complex (anistreplase); urokinase; recombinant tissue-type plasminogen activator (rtPA), which is also known as alteplase or activase; and two recombinant derivatives of rtPA, tenecteplase and reteplase. Of these, streptokinase, anistreplase, and urokinase are no longer available in the United States. All these agents act by converting plasminogen, the zymogen, to plasmin, the active enzyme (Fig. 123-7). Plasmin then degrades the fibrin matrix of thrombi and produces soluble fibrin degradation products. Endogenous fibrinolysis is regulated at two levels. Plasminogen activator inhibitors, particularly the type 1 form (PAI-1), prevent excessive plasminogen activation by regulating the activity of tPA and urokinase-type plasminogen activator (uPA). Once plasmin is gener ated, it is regulated by plasmin inhibitors, the most important of which is α2-antiplasmin. The plasma concentration of plasminogen is twofold higher than that of α2-antiplasmin. Consequently, with pharmacologic doses of plasminogen activators, the concentration of plasmin that is generated can exceed that of α2-antiplasmin. In addition to degrading fibrin, unregulated plasmin can also degrade fibrinogen and other clot ting factors. This process, which is known as the systemic lytic state,

Plasminogen activators PAI-1 Plasmin Plasminogen α2-antiplasmin Fibrin degradation products Fibrin FIGURE 123-7 The fibrinolytic system and its regulation. Plasminogen activators convert plasminogen to plasmin. Plasmin then degrades fibrin into soluble fibrin degradation products. The system is regulated at two levels. Type 1 plasminogen activator inhibitor (PAI-1) inhibits the plasminogen activators, whereas α2antiplasmin serves as the major inhibitor of plasmin. reduces the hemostatic potential of the blood and increases the risk of bleeding. The endogenous fibrinolytic system is geared to localize plasmin generation to the fibrin surface. Both plasminogen and tPA bind to fibrin to form a ternary complex that promotes efficient plasminogen activation. In contrast to free plasmin, plasmin generated on the fibrin surface is relatively protected from inactivation by α2-antiplasmin, a feature that promotes fibrin dissolution. Furthermore, C-terminal lysine residues, exposed as plasmin degrades fibrin, provide bind ing sites for additional plasminogen and tPA molecules. This creates positive feedback that enhances plasmin generation. When used phar macologically, the various plasminogen activators capitalize on these mechanisms to a lesser or greater extent. Plasminogen activators that preferentially activate fibrin-bound plasminogen are considered fibrin-specific. In contrast, nonspecific plasminogen activators do not discriminate between fibrin-bound and circulating plasminogen. Activation of circulating plasminogen results in the generation of unopposed plasmin that can trigger the systemic lytic state. Alteplase and its derivatives are fibrin-specific plasminogen activators, whereas streptokinase, anistreplase, and urokinase are non specific agents. ■ ■STREPTOKINASE Unlike other plasminogen activators, streptokinase is not an enzyme and does not directly convert plasminogen to plasmin. Instead, strep tokinase forms a 1:1 stoichiometric complex with plasminogen. Forma tion of this complex induces a conformational change in plasminogen that exposes its active site (Fig. 123-8). The streptokinase-plasminogen complex then converts

additional plasminogen to plasmin. S Plasminogen Streptokinase S Plasminogen Streptokinase FIGURE 123-8 Mechanism of action of streptokinase. Streptokinase binds to plasminogen and induces a conformational change in plasminogen that exposes its active site. The streptokinase/plasmin(ogen) complex then serves as the activator of additional plasminogen.

Streptokinase has no affinity for fibrin, and the streptokinaseplasminogen complex activates both free and fibrin-bound plasmino gen. Activation of circulating plasminogen generates enough plasmin to overwhelm α2-antiplasmin. Unopposed plasmin not only degrades fibrin in the occlusive thrombus but also induces a systemic lytic state. When given systemically to patients with acute MI, streptokinase reduces mortality. For this indication, the drug is usually given as an IV infusion of 1.5 million units over 30–60 min. Patients who receive streptokinase can develop antibodies against the drug, as can patients with prior streptococcal infection. These antibodies can reduce the effectiveness of streptokinase. Allergic reactions occur in ~5% of patients treated with streptoki nase. These may manifest as a rash, fever, chills, and rigors. Although anaphylactic reactions can occur, these are rare. Transient hypotension is common with streptokinase and has been attributed to plasmin- mediated release of bradykinin from kininogen. The hypotension usu ally responds to leg elevation and administration of IV fluids and low doses of vasopressors, such as dopamine or norepinephrine. ■ ■ANISTREPLASE To generate this drug, streptokinase is combined with equimolar amounts of Lys-plasminogen, a plasmin-cleaved form of plasminogen with a Lys residue at its N terminal. The active site of Lys-plasminogen that is exposed upon combination with streptokinase is then masked with an anisoyl group. After IV infusion, the anisoyl group is slowly removed by deacylation, giving the complex a half-life of ~100 min. This allows drug administration via a single bolus infusion. Although it is more convenient to administer, anistreplase offers few mechanistic advantages over streptokinase. Like streptokinase, anistreplase does not distinguish between fibrin-bound and circulat ing plasminogen. Consequently, it too produces a systemic lytic state. Likewise, allergic reactions and hypotension are just as frequent with anistreplase as they are with streptokinase. When anistreplase was compared with alteplase in patients with acute MI, reperfusion was obtained more rapidly with alteplase than with anis treplase. Improved reperfusion was associated with a trend toward better clinical outcomes and reduced mortality rate with alteplase. These results and the high cost of anistreplase dampened the enthusiasm for its use. ■ ■UROKINASE Urokinase is a two-chain serine protease derived from cultured fetal kidney cells with a molecular weight of 34,000. Urokinase converts plasminogen to plasmin directly by cleaving the Arg560-Val561 bond. Unlike streptokinase, urokinase is not immunogenic, and allergic reac tions are rare. Urokinase produces a systemic lytic state because it does not discriminate between fibrin-bound and circulating plasminogen. Despite many years of use, urokinase has never been systemically evaluated for coronary thrombolysis. Instead, urokinase is often employed for catheter-directed lysis of thrombi in the deep veins or the peripheral arteries. Because of production problems, urokinase is no longer available. ■ ■ALTEPLASE A recombinant form of single-chain tPA, alteplase has a molecular weight of 68,000. Alteplase is rapidly converted into its two-chain form by plasmin. Although single- and two-chain forms of tPA have equiva lent activity in the presence of fibrin, in its absence, single-chain tPA has 10-fold lower activity. Alteplase consists of five discrete domains (Fig. 123-9); the N-terminal A chain of two-chain alteplase contains four of these domains. Residues 4 through 50 make up the finger domain, a region that resembles the finger domain of fibronectin; residues 50 through 87 are homologous with epidermal growth factor, whereas residues 92 through 173 and 180 through 261, which have homology to the kringle domains of plasminogen, are designated as the first and

second kringle, respectively. The fifth alteplase domain is the protease domain; it is located on the C-terminal B chain of two-chain alteplase. The interaction of alteplase with fibrin is mediated by the finger domain and, to a lesser extent, by the second kringle domain. The

tPA F EGF K1 K2 P KHRR AAAA

F EGF K1 K2 P TNK-tPA K2 P r-PA FIGURE 123-9 Domain structures of alteplase (tPA), tenecteplase (TNK-tPA), and reteplase (r-PA). The finger (F), epidermal growth factor (EGF), first and second kringles (K1 and K2, respectively), and protease (P) domains are illustrated. The glycosylation site (Y) on K1 has been repositioned in tenecteplase to endow it with a longer half-life. In addition, a tetra-alanine substitution in the protease domain renders tenecteplase resistant to type 1 plasminogen activator inhibitor (PAI-1) inhibition. Reteplase is a truncated variant that lacks the F, EGF, and K1 domains. CHAPTER 123 affinity of alteplase for fibrin is considerably higher than that for fibrin ogen. Consequently, the catalytic efficiency of plasminogen activation by alteplase is two to three orders of magnitude higher in the presence of fibrin than in the presence of fibrinogen. This phenomenon helps to localize plasmin generation to the fibrin surface. Antiplatelet, Anticoagulant, and Fibrinolytic Drugs
Although alteplase preferentially activates plasminogen in the pres ence of fibrin, alteplase is not as fibrin selective as was first predicted. Its fibrin specificity is limited because, like fibrin, (DD)E, the major soluble degradation product of cross-linked fibrin, binds alteplase and plasminogen with high affinity. Consequently, (DD)E is as potent

as fibrin as a stimulator of plasminogen activation by alteplase. Whereas plasmin generated on the fibrin surface results in thromboly sis, plasmin generated on the surface of circulating (DD)E degrades fibrinogen. Fibrinogen degradation results in the accumulation of fragment X, a high-molecular-weight clottable fibrinogen degradation product. Incorporation of fragment X into hemostatic plugs formed at sites of vascular injury renders them susceptible to lysis. This phenom enon may contribute to alteplase-induced bleeding. A trial comparing alteplase with streptokinase for treatment of patients with acute MI demonstrated significantly lower mortality with alteplase than with streptokinase, although the absolute difference was small. The greatest benefit was seen in patients age <75 years with anterior MI who presented <6 h after symptom onset. For treatment of acute MI or acute ischemic stroke, alteplase is given as an IV infusion over 60–90 min. The total dose of alteplase usually ranges from 90 to 100 mg. Allergic reactions and hypotension are rare, and alteplase is not immunogenic. ■ ■TENECTEPLASE Tenecteplase is a genetically engineered variant of tPA and was designed to have a longer half-life than tPA and to be resistant to inac tivation by PAI-1. To prolong its half-life, a new glycosylation site was added to the first kringle domain (Fig. 123-9). Because addition of this extra carbohydrate side chain reduced fibrin affinity, the existing gly cosylation site on the first kringle domain was removed. To render the molecule resistant to inhibition by PAI-1, a tetra-alanine substitution was introduced at residues 296–299 in the protease domain, the region responsible for the interaction of tPA with PAI-1. Tenecteplase is more fibrin-specific than tPA. Although both agents bind to fibrin with similar affinity, the affinity of tenecteplase for (DD) E is significantly lower than that of tPA. Consequently, (DD)E does not stimulate systemic plasminogen activation by tenecteplase to the same extent as tPA. As a result, tenecteplase produces less fibrinogen degradation than tPA.

For coronary thrombolysis, tenecteplase is given as a single IV bolus. In a large phase III trial that enrolled >16,000 patients, the 30-day mor tality rate with single-bolus tenecteplase was like that with acceleratteddose tPA. Although rates of intracranial hemorrhage were similar with both treatments, patients given tenecteplase had fewer noncerebral bleeds and a reduced need for blood transfusions than those treated with tPA. The improved safety profile of Tenecteplase likely reflects its enhanced fibrin specificity.

■ ■RETEPLASE Reteplase is a single-chain, recombinant tPA derivative that lacks the finger, epidermal growth factor, and first kringle domains (Fig. 123-9). This truncated derivative has a molecular weight of 39,000. The affinity of reteplase for fibrin is lower than that of tPA likely because reteplase lacks the finger domain. Because it is produced in Escherichia coli, reteplase is not glycosylated. This endows it with a plasma half-life lon ger than that of tPA. Consequently, reteplase is given as two IV boluses, which are separated by 30 min. Clinical trials have demonstrated that reteplase is at least as effective as streptokinase for treatment of acute MI, but the agent is not superior to tPA. CONCLUSIONS AND FUTURE DIRECTIONS Thrombosis involves a complex interplay among the vessel wall, platelets, the coagulation system, and the fibrinolytic pathways. Acti vation of coagulation also triggers inflammatory pathways that may exacerbate thrombosis. A better understanding of the biochemistry of blood coagulation and advances in structure-based drug design have identified new targets and resulted in the development of novel anti thrombotic drugs. Well-designed clinical trials have provided detailed information on which drugs to use and when to use them. Despite these advances, however, thromboembolic disorders remain a major cause of morbidity and mortality. Therefore, the search for better and safer targets continues. PART 4 Oncology and Hematology

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